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AN INTRODUCTION TO ORGANIC CHEMISTRY

By

ROGER J. WILLIAMS

and

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The University of Texas

FIFTH EDITION



D. VAN NOSTRAND COMPANY, INC.

TORONTO

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PREFACE TO THE FIFTH EDITION

In the preparation of the fifth edition of this widely used book the authors have adhered to the fundamental philosophy on which its original writing was based, namely, the desire to develop insight on the part of students rather than encourage them *merely* to accumulate factual data.

In order to emphasize the reasonableness that underlies much of organic chemistry rather than the innumerable hard facts that must be committed to memory, it is necessary to introduce consistently the unknown in terms of what may presumed to be already known. In order to do this we avoid wherever possible bringing into the discussions unfamiliar compounds and phenomena of which the student can know very little. For example, if a student is expected to absorb when he reaches page 10 the fact that methane may be obtained by using a Grignard reagent, it becomes at once obvious that a *superficial* knowledge is the paramount demand. If the student is told that acetone is CH_3COCH_3 before he has the background to understand the formula, he is thereby informed very effectively that he is expected to memorize and not to understand or think. The attempt to promote and preserve a critical and thinking attitude on the part of students is by no means easy nor is it universal. We have sought in this revision to produce a text which will be helpful rather than one which will militate against maintaining a healthy student attitude in this regard.

The main task of this revision is to bring the material up to date. Organic chemistry is a rapidly developing science. Atebrin, DDT, gammexane (666), sodium monofluoroacetate, fluorocarbons, Freons, 2,4-dichlorophenoxyacetic acid (2,4-D), penicillin G and folic acid are examples of new compounds which are introduced, and newer developments in the fields of detergents, elastoplastics, high polymers, weed killers, rodenticides, plant hormones, antibiotics and insecticides are included. Among

the topics which have received a more extended treatment are: chemical reactivity in relation to atomic structure, use of isotopic tracer elements, alkyl halides, unsaturated hydrocarbons and acids, petroleum, nitroparaffins and sulfur compounds. The modern trend toward the utilization of petroleum as a source material for aliphatic and aromatic chemicals as well as newer methods of preparation in general and newer uses are given due prominence. The production figures, tabular information and the periodic table are brought up to date, and the nomenclature is brought into line with that adopted by chemical abstracts.

The authors will appreciate having errors called to their attention and will welcome criticisms which are aimed at improving the text.

ROGER J. WILLIAMS
LEWIS F. HATCH

PREFACE TO FIRST EDITION

The desire to rationalize more fully the subject of organic chemistry is the basic reason for the existence of this text book. The author fully realizes that it is not yet possible to reason successfully about all of the phenomena of organic chemistry. However, most of the reactions, especially of the simpler compounds, take place in a manner which can be predicted, at least roughly, by means of acceptable theories and in the light of the behavior of related compounds. In general, the author has attempted to point out these relationships and has made them an important part of the discussions. Care has been taken, however, to avoid the use of any theory unless it is in good standing and gives definite promise of some permanence.

It has seemed natural and desirable that organic chemistry be related to inorganic and theoretical chemistry as much as possible in order that the whole subject be unified. Through the use of the Lewis theory of valence and atomic and molecular structures, and the introduction of some conceptions of his own in regard to the classification of compounds, the author feels that some progress has been made in clarifying and utilizing the natural connection between organic chemistry and the other branches of the science. The details of this feature cannot be discussed in a short space, so the reader must judge of its value after an examination of the text. It appears frequently, as an integral part of the treatment.

A scientific approach to a subject demands that the student shall not form the habit of accepting statements unquestioningly on mere authority. For this reason the author has avoided making statements and presenting discussions which the student, because of his lack of preparation, must accept uncritically if at all. An attempt is made to present the material in a connected and understandable story, and in so doing it has been necessary to introduce new substances only in terms of substances already

studied. Especially in the first part of the book, each compound or group of compounds is studied from the standpoint of chemical behavior. The discussion of methods of formation and preparation which involve strange compounds is postponed until the student is in a position to grasp their significance. As the study progresses and the student's acquaintances multiply, it becomes no longer necessary to delay full discussions, since they are not so likely to involve the consideration of totally strange substances.

In addition to the distinctive features already cited, there are several of minor importance which may be mentioned. For example, brief general discussions are given of a number of topics which are outside the scope of formal organic chemistry, in order to broaden the student's appreciation of the many points of contact of this special branch of knowledge. These topics include; solubility relationships, cleansing action of soaps, explosives, general properties of colloidal solutions (in connection with proteins), enzyme action, action of indicators, etc. To give some slight historical background without the expenditure of extra time, short biographical footnotes are inserted concerning the chemists who are mentioned in the text.

The problems at the end of each chapter are designed to test the student's understanding of the subject and his resourcefulness in applying it. The solution of the problems involves application rather than repetition of the material presented in the chapter. In some cases entirely new lines of thought are suggested. Numerical answers to problems are given in Appendix I.

The physical constants of compounds and solubility data are most often given in tables, which are distributed throughout the text. There are tables giving not only the ionization constants of various acids and bases but also their percentage ionization in .1 N solution. This latter figure is introduced because it has a more definite and tangible meaning to the average student of organic chemistry.

References are made to numerous books where the interested student may obtain further information along particular lines. In these cases the author has tried to select books which the student can read understandingly, rather than the most exhaus-

tive treatises. A few references to journal literature are cited for use of the instructor and any students who may have occasion to use them. In Appendix II is given a short discussion on how to use standard works and journals for reference purposes.

Because of the limited amount of time available, instructors will ordinarily follow the practice of omitting from assignments and class-room discussions, certain chapters or parts of chapters. It is suggested that when the text is used for shorter courses for medical students, only a few omissions be made of the material presented in the first thirteen chapters, but that frequent omissions be made thereafter. With medical students little emphasis should be placed upon subject matter which is only of technical importance. For this reason some instructors will find it advisable to omit a large part of the material dealing with the aromatic compounds, and to devote additional time to the chemistry of proteins and carbohydrates. These complex and biologically important compounds are treated in this text more fully than usual. Material which is to be used primarily for reference, and also subject matter which is extrinsic to the general development of the subject, is placed in fine print. In spite of the care taken, errors will undoubtedly be found in the text. The author will appreciate having them called to his attention.

ROGER J. WILLIAMS

EUGENE, OREGON,
March 31, 1927.

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It is difficult to mention all the sources from which have come help and inspiration for the preparation of this book. For my interest and grounding in the subject of organic chemistry I am indebted to a large extent to the very stimulating lectures of Professor Julius Stieglitz at the University of Chicago during 1917 and 1918. I wish to thank my colleagues for the help and encouragement which they have given in many ways. Dr. F. L. Shinn especially has given much of his time to discussing with me various novel ideas and has been of great assistance in developing what I hope is a sane attitude. He has also read critically considerable portions of the manuscript. Mr. John L. Wilson my assistant has been of great service in going over the entire manuscript. I am indebted to my wife Hazel E. Williams, who also went over the entire manuscript and has given much in the way of inspiration and encouragement. My thanks are due Mr. W. H. Strain, graduate student at Massachusetts Institute of Technology, Professor Lauder W. Jones of Princeton University, and Professor Howard J. Lucas of the California Institute of Technology, all of whom have read the manuscript and have made valuable criticisms and suggestions. Especially do I express my gratefulness to my brother Robert R. Williams, Chemical Director of the Bell Telephone Laboratories, Inc., of New York, who has given much constructive criticism and has helped generously in many ways to make the book possible.

March 31, 1927

ROGER J. WILLIAMS

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CHAPTER I

INTRODUCTION—MOLECULAR FORMULAS

The materials and phenomena studied in the field of organic chemistry are very closely associated with our daily activities. We might study the clothes we wear, the dyes that color them, the soap, starch and bluing used in the laundry, the leather in our shoes, the dye and the shoe polish, without leaving the domain of organic chemistry. The wood we use for building our houses and furniture, as well as the paints and varnishes used for finishing, might be a subject of our study as well as the fuel used to warm our houses and propel our automobiles. The paper from which our books are made and the ink used for printing and writing might also engage our study. The products of organic chemistry are the basis of the photographic and moving picture industries.

Organic chemistry has much to do not only with the machinery (gaskets, belts, composition gears, electrical insulation, safety glass, etc.) which is at the basis of modern life, but enters into the make up of an interminable list of fabricated articles including those made from natural or synthetic rubber and plastics. The artificial textiles, rayon, nylon, etc., are products of organic chemistry and are of growing importance. Even the explosives that civilization uses for self-destruction (as well as for many more worthy causes) are most often organic chemicals.

Much of the continual change going on in our bodies in the metabolism of foods and in growth and maintenance of our bodily functions involves organic chemistry, as do the analogous changes taking place throughout the whole biological world, plant and animal. By far the greater part of our food is organic in nature as are the majority of useful drugs. The entire chemistry of plant and animal physiology, including the increasingly important emphasis on vitamins, hormones, and enzymes, is to a large extent applied organic chemistry.

2 INTRODUCTION TO ORGANIC CHEMISTRY

However, many of the substances and topics mentioned above are of such a complex nature that a large background of study is necessary before one can grasp the problems involved. It is therefore necessary first to build a foundation of elementary facts and principles as a basis for further study.

Meaning of "Organic" Chemistry. An "organic" substance, as the term was originally applied, meant a chemical substance present in and obtainable from plant and animal organisms but not obtainable from mineral or other inanimate sources. Today the term is applied to any substance which contains the element carbon, though some compounds such as carbonates, which are common in the mineral world, are generally treated in the field of inorganic chemistry. The organic compounds which will engage our study include not only many substances which were obtained first directly from animate sources, but also many more which have been built up in chemical laboratories and which never existed on earth previous to their artificial synthesis. Many of the compounds originally recognized as of animate origin can now be produced in the laboratory. Synthetic organic products are so common that we no longer think of organic chemistry as being connected in a distinctive way with organisms.

Distinctive Features of Organic Chemistry. A complete picture of the distinctiveness of organic chemistry cannot be grasped without studying the subject for an extended period. However, the more crucial points are understandable at the outset of such a study.

Large numbers of compounds. Of the total number of known compounds of all elements (which approaches a half million) nearly 90 per cent are *organic* compounds, *i.e.*, they contain carbon. For reasons which will be more apparent later, carbon is capable of acting as a building unit to a degree much beyond that of any other element. Of the new compounds being discovered (an average of several each day) more than 90 per cent contain the element carbon.

Types of compounds and reactions. In the study of inorganic chemistry in its fundamental phases, emphasis is rightly placed upon the *acids*, *bases*, and *salts*. In the field of organic chemistry there are more acids, more bases, and more salts than

in all other branches of chemistry combined, and they follow, in general, exactly the same laws as apply to inorganic acids, bases, and salts. But a very large number of organic compounds are *not* distinctively acids, bases or salts; instead they are more analogous to less common inorganic compounds which are not often studied. The reactions which are studied and stressed in the field of organic chemistry are *not* those which take place typically between acids, bases and salts, though actually these reactions are made use of daily by the organic chemist.

General characteristics of carbon compounds. While organic compounds comprise a large and somewhat heterogeneous group they have some properties in common. They almost invariably burn; inorganic compounds may or may not do so. Carbon compounds in comparison with most inorganic substances, decompose more readily by heating in the absence of air. Many organic compounds are volatile but salts whether organic or inorganic are relatively non-volatile (organic salts decompose before they volatilize). Organic reactions have the reputation of being relatively slow—this excludes, however, the reactions between organic acids, bases, and salts which take place with great speed just as among the inorganic compounds. Organic compounds are sometimes said to be non-ionized. This, however, excludes the numerous organic acids, bases, and salts, all of which are ionized.

Due to the fact that organic molecules are often complex, reactions involving them may likewise be complicated. In most cases it is not possible to picture quantitatively what happens in a reaction vessel by the use of a single equation.

Importance of atomic arrangements. Whereas in inorganic chemistry the simple formulas used represent perfectly definite chemical substances, we find in organic chemistry even such a simple formula as C_2H_6O may be applied with equal appropriateness to two different compounds. There are two ways in which the atoms represented can be arranged to form two different kinds of molecules. In this case and in thousands of others we not only know with a reasonable degree of certainty what the different arrangements are, but it is possible by methods which will be made clear later to ascertain which arrangement belongs to each

particular substance. In some cases there are as many as a hundred or more possible arrangements and a corresponding number of compounds with the same composition, and yet we can be certain which of the particular substances has each of the possible atomic arrangements. The determination of the arrangements of atoms in molecules is one of the most important features of the study of organic compounds.

Compounds of Elements Closely Related to Carbon. The distinctiveness of carbon as an element is striking but it does not stand out as a single, isolated case. Below are listed the members of the first two (short) periods of the periodic table. The number below each symbol is that of the known number of hydrides of the element, and the chart illustrates the fact that the elements most closely related to carbon tend to approach it (though afar off) in its ability to act as a building unit for stable compounds. The figure for the number of hydrides of carbon is somewhat misleading because, while it represents the approximate number of compounds which have been purified, it does not convey the fact that by using known methods chemists could multiply the known hydrides of carbon many times if they chose to spend the requisite time.

He	Li	Be	B	C	N	O	F
0	1	1	7	about 2500	6 or 7	2	1

Ne	Na	Mg	Al	Si	P	S	Cl
0	1	1(?)	—	9	6	5	1

Molecular Formulas. Before proceeding to the study of specific organic compounds where problems of molecular structure are very prominent, it is necessary for the student to have clearly in mind the elementary facts regarding analysis and molecular weight determinations. The determination of the molecular formula of a compound must precede the study of how the atoms are arranged within the molecules.

The principles involved are exactly the same as in inorganic chemistry. We must first deal with a pure compound rather

than a mixture; the percentages of the different elements must be determined; from these the *empirical* formula can be calculated. The empirical formula alone, such as CH_2O , is of comparatively little value in organic chemistry because hundreds of compounds are known which yield this same result upon analysis. Only by molecular weight determination can one decide whether the molecules of the compound in question are correctly represented by CH_2O or whether they are represented by $\text{C}_2\text{H}_4\text{O}_2$, $\text{C}_3\text{H}_6\text{O}_3$ or some higher multiple.

Purity. It is first necessary, before we study a compound, to be sure that it is a reasonably pure substance. If a substance melts sharply at a given temperature, and, after attempts to purify, melts at the same temperature, it can be assumed to be a pure compound. A constant boiling point is not as good as a criterion of purity because there are numerous so-called azeotropic mixtures which have constant boiling points. Alcohol, 95 per cent, and water, 5 per cent, constitute such a mixture. In this and many other cases the constituents of the constant-boiling mixtures may be separated by chemical means.

Elementary discussions and laboratory exercises dealing with the purification of organic compounds by recrystallization and distillation are presented in the laboratory manual accompanying this text and will not be given here.

Analysis to determine the elements present. (*Qualitative analysis.*) Organic compounds may contain almost any element but as a rule few elements are present and elaborate tests are unnecessary. The methods whereby carbon, hydrogen, nitrogen, sulfur, phosphorus and halogens may be detected are outlined in the laboratory manual. There is no satisfactory qualitative test for oxygen and its presence is recognized only after a quantitative analysis.

Quantitative analysis. For the quantitative determination of carbon and hydrogen the compound is burned usually in the presence of copper oxide, under such conditions that the carbon dioxide and water formed may be collected separately and weighed. The essentials of the method were worked out by

Liebig¹ in 1831 and have been subjected to many modifications since that time. Experience in recent years has shown that the most rapid and convenient methods of analysis for carbon and hydrogen are the so-called "micro" methods in which the samples burned weigh less than 10 milligrams, and the weighings are made on micro-balances which are sensitive to one microgram (1γ). These methods are applicable to all types of compounds but are indispensable when the compounds to be analyzed are rare or expensive.

Usually oxygen is not determined directly but its percentage is calculated from the difference between the weight of the original sample and the sum of the weights of all the other elements found.

Oxygen can be determined by carrying out the "combustion" catalytically in the presence of hydrogen and weighing the water that is formed (Ter Meulen). Oxygen can also be determined by "oxidation equivalent analysis" (Williams) in which the oxygen required for complete oxidation of a compound is found. If the molecular weight of a compound is known and the oxygen required for combustion is found, the complete formula may be calculated. For the compound $C_xH_yO_z$ with molecular weight M , and which requires N atoms of oxygen per molecule for complete combustion, $x = (M - 2N - 18z)/8$; $y = (6N - M + 22z)/2$; and $z = (M - 6N + 2y)/22$. Since x , y , z , M , and N are integers, the equations can be solved.

Nitrogen may be determined by a combustion in which case the nitrogen gas is evolved and measured as such (Dumas² method). It may also be determined by the Kjeldahl method (p. 314) which involves oxidizing the compound with concen-

¹ J. von Liebig (1803-1873) was a pioneer organic chemist in Germany. He also worked in the field of agricultural and food chemistry, and was the founder of an important early chemical journal, "Liebig's Annalen." His name is associated in the popular mind with "Liebig's Extract of Beef."

² Jean B. A. Dumas (1800-1884) was a French chemist. In addition to originating this method for determining nitrogen he was also responsible for a direct method of vapor density determination which has been widely used. He was a skillful experimenter and a brilliant thinker. Much of his energy in later life was devoted to public service in the fields of education, public health, etc.

trated sulfuric acid, and determining the ammonia produced. This method is not applicable to all compounds (p. 315).

The results of analysis make possible the calculation of the empirical formula. Dividing the percentages of the various elements by their respective atomic weights gives values expressing the relative proportions of the different atoms present. By converting these to simple whole numbers the empirical formula is derived. This process should already be familiar to the student.

Molecular weights. The most important general method for determining the molecular weights of organic compounds is the "freezing point" method. The "boiling point" method is used to some extent, and for very simple volatile compounds the vapor density method is applicable. The osmotic pressure method, while theoretically useful and extremely sensitive, is very seldom used because of experimental difficulties connected with the preparation of suitable membranes.

Each solvent is affected to a different degree when one mole of an undissociated substance is dissolved in it. One mole in 1000 grams of water lowers the freezing point 1.86° . The corresponding freezing point lowering for benzene is 4.9° , for acetic acid 3.9° , for phenol (carbolic acid) 7.6° , for dioxan, 4.7° . Camphor has the extraordinarily high "constant" of 40° , and has been used extensively for molecular weight determinations in recent years. A relatively concentrated solution of the substance in camphor is prepared and solidified. Its melting point is then determined by the usual methods inasmuch as the constant for camphor is so high as to even obviate the necessity of using a Beckmann thermometer.

The effects on the boiling points of dissolving a mole of solute in 1000 grams of solvent are less than on the freezing points. The small rise in boiling point makes the method less sensitive. The "constants" for various solvents are: water 0.52° , acetic acid 2.53° , benzene 2.67° , carbon disulfide 2.37° , ethanol 1.15° .

Some solvents have a tendency to "associate" molecules into double and triple molecules, and a molecular weight, which is too high, results. This difficulty can be overcome frequently by trying different solvents and assuming the lowest results to be more nearly correct provided the substance is not an electrolyte.

Usually molecular weights are not determined accurately by these methods, because an approximate value, in conjunction with analytical results, is sufficient to determine the correct value.

A simple method of calculation which can be used as a basis for comprehending molecular formulas involves first a thorough appreciation of what a mole is, and how, even in the case of an unknown compound, the amount constituting a mole can be determined.

With this understanding as a ground work one may deduce that (1) the number of carbon atoms in a compound is equal to the number of moles of carbon dioxide produced by the burning of *one mole* of the compound, (2) the number of hydrogen atoms is equal to twice the number of moles of water produced, (3) the number of nitrogen atoms is equal to twice the number of moles of nitrogen produced (Dumas). To utilize units which are closer to the experimental ones, millimoles (thousandths of moles) are preferable, in which case statements (1), (2), and (3) hold, provided the term *millimole* is substituted in each case for *mole*. A millimole in the gaseous state at standard conditions occupies 22.4 cc. and lowers the freezing point of 1 ml. of water 1.86°.

PROBLEMS³

1. A substance, weight 0.40 g., dissolved in 9 g. of benzene, raised the boiling point 0.4°; calculate the molecular weight of the substance.

2. A sample of camphor melted at 177°; a mixture of 5.5 mg. of an unknown substance with 50 mg. of the camphor melted at 154°. What is the molecular weight of the unknown?

3. (a) If an aqueous solution containing one gram of a non-volatile substance per 100 g. of water freezes at -0.140° , what is the molecular weight of the compound? (b) How much would the freezing points of the following solvents be lowered by the presence of 1 g. of the same substance in 100 g. of solvent (1) benzene, (2) acetic acid? (c) What would be the actual boiling points of these solutions? Assume that no dissociation or association takes place in any case.

4. How would the freezing points of one molar solution of (a) a salt, (b) a non-electrolyte, and (c) a weak acid, compare?

5. Pure phenol freezes at 43°. What would be the freezing point of phenol which has taken up one-fifth per cent of its weight of water from the air?

³ In order to grasp and retain the material presented in a course in organic chemistry it is very necessary that the student do something more than read and re-read the text. Beginning with the first assignment he should prepare *written* outlines and summaries of the material he wishes to learn. In addition he should solve problems which involve applying the principles to concrete cases.

6. A substance in dilute solution is capable of exerting approximately as much osmotic pressure as it would be able to exert gas pressure if it were in the gaseous-state. A mole of sugar in 22.4 liters of solution is thus capable of exerting an osmotic pressure of 760 mm. of mercury (one atmosphere). How many mm. of mercury would be supported by the osmotic pressure of a 2 per cent solution of a substance with a molecular weight of 1200? How many cm. of water would this same pressure support? What would be the freezing point of the solution?

7. A compound was found to contain carbon and hydrogen, and a test for no other element was obtained. On analysis it was found to contain 48.56 per cent carbon, 3.06 per cent hydrogen. What is the empirical formula for the compound? 1.69 g. of the substance when vaporized gave 375.2 cc. of vapor at 760 mm. and 0° . What is the molecular formula?

8. A sample of a substance weighing 0.200 g. gave upon combustion 0.189 g. of carbon dioxide and 0.077 g. of water. The sulfur in a sample of the same substance was converted into barium sulfate. 0.153 g. of the substance gave 0.769 g. of BaSO_4 . What is the empirical formula of the substance?

9. If sodium acetate is 28.4 per cent sodium, and acetic acid has the empirical formula CH_2O , what is the lowest molecular weight that the acetic acid can have? (Assume various formulas and calculate percentages.)

10. Chlorophyll (an organic compound) contains 2.72 per cent magnesium. What is the least molecular weight it can have?

11. In the Dumas method for the determination of nitrogen the compound is oxidized with copper oxide in an atmosphere of carbon dioxide under such conditions that the nitrogen is evolved as such and is measured directly. How many cc. of moist nitrogen at 25° and 750 mm. would be obtained from 0.182 g. of a substance having the molecular formula $\text{C}_6\text{H}_7\text{N}$?

12. Calculate from the following data the atomic volumes, in ml. per gram atom, of the following elements (in the state specified):

	Atomic Weight	Density (g. per ml.)
C	12.00	2.25 (graphite)
Cl	35.46	1.56 (liquid Cl_2)
Br	79.92	3.12 (liquid Br_2)
F	19.00	1.11 (liquid F_2)

13. One millimole of an unknown compound, determined experimentally to be 90 mg., is found to yield on burning 132 mg. of CO_2 , 90 mg. of water and 22.4 cc. of nitrogen at standard conditions. What is the molecular formula of the compound?

CHAPTER II

SATURATED HYDROCARBONS

(Alkanes, Paraffins)

The organic substances which we shall study first are among the simplest, in that they contain only one element other than carbon, namely, hydrogen. It is not for this reason alone that the hydrocarbons are considered first, but also because many other compounds can be prepared from them. The hydrocarbons are structurally related to numerous other organic substances which may be considered profitably as hydrocarbon derivatives.

Before discussing the molecular structures and behavior of the hydrocarbons, it will be desirable to review briefly what chemists have learned about atomic structure in its relation to chemical behavior. A thorough acquaintance with these fundamental ideas which chemists have arrived at after decades of intensive study is of greatest value in helping to understand better not only the characteristics of hydrocarbons but of all organic (as well as inorganic) compounds.

Atomic Structure and Chemical Reactivity. The present theory of atomic structure pictures every atom as being a sub-microscopic solar system in which negatively charged electrons are revolving about a positively charged nucleus. Essentially all the mass of atoms is in the nucleus. The electrons of all elements are identical but the nuclei of the atoms of one element differ from those of another in charge and in mass. The *chemical* properties of an atom are determined by the electrons in the outermost shell which for a free atom never exceed eight in number. These electrons are called "valence" electrons.

A basic concept of nature is that all changes which take place in the universe do so in such a way that greater stability is attained as a result. If chemical reactions involve essentially

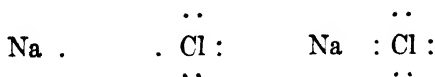
the valence electrons, then chemical changes may be postulated to take place in such a way that a greater electronic stability results. It follows that the most stable electronic configurations will be found in the most unreactive elements. These elements are the inert gases helium, neon, argon, krypton, etc. Physical methods have demonstrated that in helium atoms there is but one shell of electrons (the K shell) and only two electrons in it. Neon, argon and krypton have 2, 3, and 4 concentric shells respectively. These are known as the L, M and N shells, the outermost of which always contains eight electrons. From these observations it is concluded that an eight-electron shell (an octet) constitutes a highly stable configuration.

On the basis of these and related findings, chemists have evolved much clearer ideas of why atoms react. The fundamental basis for reactions is that every atom strives to attain a stable electron configuration like that of an inert gas. Another fundamental principle which helps us understand why reactions do or do not take place is that electrons have a strong tendency to form pairs (rule of two).

Atoms may attain an electronic structure similar to that of an inert gas in two different ways. An *ionic* bond may be formed by the complete transfer of an electron from one atom to another. A *covalent* bond results when atoms share two electrons between them. In the latter case the two electrons are in both shells, they are effective in completing a stable electronic configuration for both atoms and the atoms are held together because of the stability arrived at in this manner.

Ionic bonds. An atom containing less than four electrons in its outer shell tends to *lose* these electrons and become a positively charged ion with a structure similar to the inert gas preceding it in the periodic system. An atom with four or more electrons in the outer shell does not lose these but may, especially in the case of those atoms possessing 5, 6 or 7 electrons in the outer shell, *take up* electrons and become a negative ion similar to the next inert gas with a higher atomic number. This type of electron transfer is illustrated by the reaction between sodium and chlorine.

When a sodium atom reacts with a chlorine atom, the sodium gives up its single outer (M shell) electron leaving an inner L shell complete with eight electrons. The chlorine atom originally with seven electrons in the M shell takes up the electron given off by the sodium and completes its octet, thus forming a stable structure.

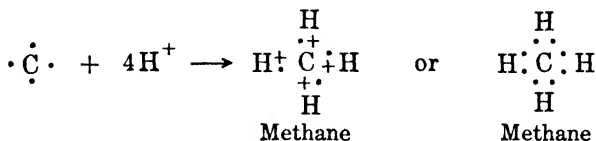


In spite of the fact that the two particles formed are electrically charged ions the reaction above is accompanied by a large loss of free energy and sodium ions and chloride ions *together* are in a very stable condition. Either ion by itself would possess high energy because of the electrical charge carried. Sodium chloride may be spoken of as an *ionic* compound and the attraction of the ions for each other is electrostatic. In our later discussions many organic reactions will be cited which take place by virtue of the fact that sodium chloride, a highly stable product, is formed and that in its formation there is a large decrease in free energy. We may go so far as to say that almost any reaction, which is capable of yielding sodium chloride (or similar halide) as a product, can be made to take place.

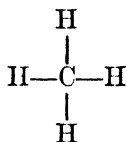
Covalent bonds. An atom such as carbon which contains four electrons in its outer shell tends neither to lose nor gain electrons but instead to gain stability by *sharing* electrons with other atoms, *e.g.*, hydrogen, halogens, oxygen, nitrogen, sulfur or other carbon atoms. The striking ability of carbon atoms to share electrons with other carbon atoms makes possible long chains of carbon atoms and the existence of the numerous hydrides of carbon referred to in Chapter I.

Methane, the simplest of the hydrocarbons, illustrates this type of linkage. A carbon atom requires four additional electrons in its L shell to complete its octet whereas each hydrogen atom requires one electron to complete its K shell. Complete electron transfer from hydrogen to carbon would not give hydrogen a structure like helium, an inert gas. However, if the electrons of four hydrogen atoms could remain in the K shell of

the hydrogen atoms and at the same time occupy positions in the L shell of the carbon atom, the carbon would attain a structure like neon and be stable. The hydrogen atoms would at the same time each share an extra electron of the carbon atom to attain a structure like helium.



Bonds of the type illustrated are relatively stable and the compounds containing them show less tendency to react chemically than might be expected. The binding force arising from a shared pair of electrons is localized and exerted in a definite direction about the atom, giving rise under appropriate conditions to phenomena which will be described later (p. 259). Because of this localization the shared electron bond is usually represented by a single bond or tie. The methane formula thus may be written

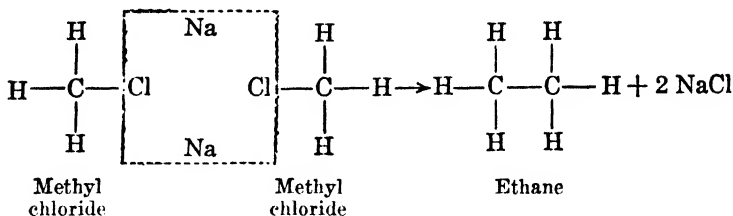


It should always be kept in mind that the "single bond" in organic chemistry represents two electrons.

Structural relationships. We have represented the molecule of methane as having the hydrogen atoms symmetrically placed around the carbon atom. This is definitely an assumption and should not be accepted as fact until it is supported by further evidence.

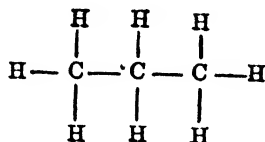
Ethane, C_2H_6 , occurs in variable amounts in natural gas and is shown to have the molecular formula indicated, by its vapor density and analysis. Since it can be produced from methyl chloride (CH_3Cl , a compound formed by replacing a hydrogen atom of methane with a chlorine atom) and metallic sodium

according to the equation (Wurtz reaction)¹ $2\text{CH}_3\text{Cl} + 2\text{Na} \rightarrow \text{C}_2\text{H}_6 + 2\text{NaCl}$, it is a reasonable assumption that its formula is as represented.



The fact that only one ethane has ever been produced by any means lends support to the symmetrical structure of methane, since if the hydrogen atoms in methane were anything but equivalent to each other, chemists would surely have been able to replace the different hydrogens by $-\text{CH}_3$, and thus have yielded different ethanes.

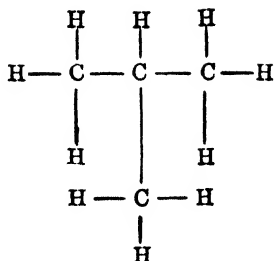
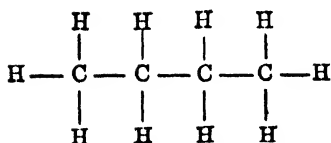
In a similar manner a plausible propane formula (C_3H_8) can be constructed as follows:



by replacing one of the equivalent hydrogens by a carbon holding three hydrogens. On this basis only one propane formula is possible.

The formula for the next member of the series, C_4H_{10} , butane, on the basis of previous assumptions, can be constructed in two different ways since the hydrogen atoms in propane are obviously not all equivalent. The two hydrogens attached to the central carbon atom are differently situated from the other six. The butane formulas are:

¹ C. A. Wurtz (1817-1884), a French chemist, discovered this reaction in 1855. Like many of the earlier chemists, he worked in several fields of chemistry. He was a student with Liebig and was later for many years professor at the Sorbonne in Paris.



Our assumptions have led us to the conclusion that there are *two* butanes with the structures indicated.

Continuing in the same manner and on the same assumptions we are led to conclude the possible existence of *three* pentanes (C_5H_{12}), *five* hexanes, (C_6H_{14}), *nine* heptanes (C_7H_{16}), and *eighteen* octanes (C_8H_{18}).

These conclusions have been completely verified experimentally since in every case the exact number required by theory (and no more) is known. Substances with the same molecular formulas, but with different structures are known as *structural isomers*. The two butanes (isomers) boil at -0.55° and -11.7°C ., and each of the 18 isomeric octanes has a boiling point within the range of 99° - 126°C . The fact that the predictions on the basis of the assumptions are completely verified, gives us confidence that the original assumptions were valid and that the structures of the hydrocarbons are fundamentally correct.

Since it is possible to build up hydrocarbon molecules with many more than eight carbon atoms per molecule it is interesting to note how the number of theoretically possible isomers increases with increase in the number of carbon atoms. See table, next page.

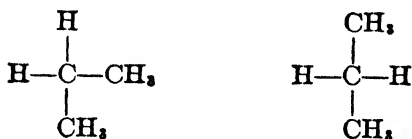
Most of these figures (Henze) are of purely academic interest because experimental verification either by building up the compounds or separation from natural sources (assuming they exist) would in most cases be utterly out of the question from the standpoint of expenditure of time. However, it is worthy of note that since a paraffin base kerosene contains hydrocarbons with from 9 to 18 carbon atoms, it may theoretically contain tens of thousands of distinct species of molecules.

NUMBER OF ISOMERIC PARAFFIN HYDROCARBONS

Molecular Formula	Number of Structural Isomers
C_9H_{20}	35
$C_{10}H_{22}$	75
$C_{11}H_{24}$	159
$C_{12}H_{26}$	355
$C_{13}H_{28}$	802
$C_{14}H_{30}$	1,858
$C_{18}H_{38}$	60,523
$C_{20}H_{42}$	366,319
$C_{30}H_{62}$	4,111,846,763

Spacial Arrangement of Atoms in Hydrocarbon Molecules.

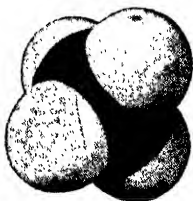
The formulas which we have used for methane, ethane, etc., have been pictured in two dimensions only, whereas we know that aggregates of matter which are composed of molecules occupy three dimensions. Any picture of the arrangement of atoms in molecules which is limited to two dimensions must be imperfect. A strict interpretation of the two-dimensional formula of methane would predict the possibility of two isomeric propanes, while only one such substance exists. The two arrangements would be as follows:



If we change our symmetrical two-dimensional methane formula into a symmetrical three-dimensional formula, we find that this difficulty of interpretation is avoided and the models predict the correct number of isomers. The symmetrical arrangement of four hydrogen atoms around a single carbon atom would be such that if the carbon atom were considered at the center of a sphere, the hydrogen atoms would be spaced equally on the surface of the sphere. In the model pictured each hydrogen atom is equally distant from the carbon, each hydrogen atom is equally distant from each of the other hydrogen atoms, and

the angle between any two hydrogen atoms is the same as that between any other pair. In terms of such a model only one propane would be possible, and if we were to construct like models for the other hydrocarbon molecules, we should find that the correct number of isomers is predicted in all cases.

However, the formulas on a plane surface are easier to interpret, are much easier to work with, and if used correctly are generally satisfactory. They should be regarded, however, as projections on a plane surface of the three-dimensional structure, and since molecules are free to rotate, no significance is placed upon whether any particular valence bond is pointed up, down, toward the left, or toward the right.

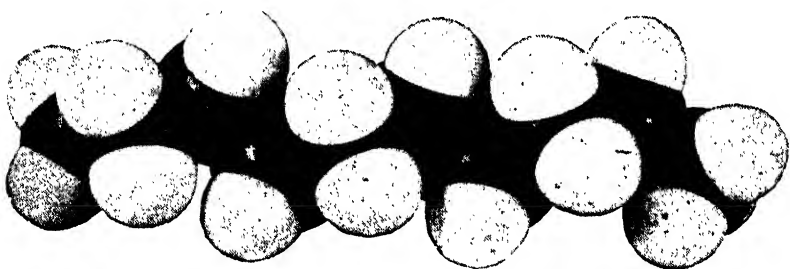


Model of Methane Molecule

We often speak of straight chain hydrocarbons. This should not be interpreted to mean that they are actually in a straight chain but rather in a continuous chain. The carbon chains are zigzag in hydrocarbon molecules and physical studies have shown that they are rolled up into loose helices.

Physical methods involving X-ray diffraction, etc., have given chemists rather definite information regarding the distances between the centers of atoms in molecules as well as the valence angles. In paraffin hydrocarbons, for example, the distance between centers of the carbon and hydrogen atoms is 1.06 Angstrom units while that between two adjacent carbon atoms as in ethane is 1.54\AA ($1\text{\AA} = 10^{-7}\text{ mm.}$). The "sizes" of constituent atoms in molecules are known with less precision. In fact the apparent size depends in part upon the method of measurement. The atoms can be distorted and when two are joined together

the distance between their centers is not equal to the sum of their radii when uncombined. The space which an individual atom occupies depends not only upon what kind of atom it is, but also upon what it may be joined to, the nature of the bonds, and the attraction of the resulting molecules for each other (internal pressure). For our present purpose we may say that carbon and hydrogen atoms in paraffin hydrocarbons have about the same radii, approximately 1\AA . Two carbon centers do not come as close together, however, as can a hydrogen and a carbon.

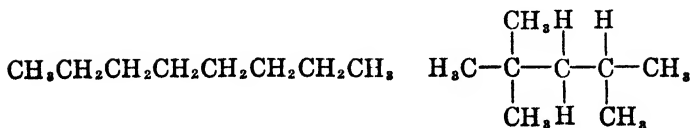


Model of Decane Molecule

Structures of Higher Hydrocarbons. There are a few notable structural features which become evident when we picture the structures of higher members of the methane series. For this purpose and in order to conserve space we shall not indicate each separate atomic symbol, but will group together hydrogen atoms which are attached to the same carbon atom.

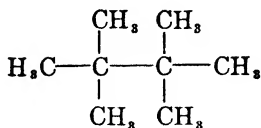
Among the 18 known octanes are those represented by the following¹:

¹ It is very desirable that the student have practice in writing full structural formulas. It is therefore suggested that he make it a habit of study to have pencil and paper always at hand for this purpose. The formulas mentioned at this point should be worked out and it is further suggested that formulas and equations which are written in abbreviated form in the text or tables should be written out in full by students. In addition equations for reactions involving homologous substances should also be written. The more practice the student has the better, and the more difficult the subject is for the student the more need of practice. See also footnote, p. 8.



I

II



III

The first, known as normal octane, is referred to as a "straight chain" hydrocarbon, but as we have already indicated this designation may be misleading. The second (with a branched chain) is a highly important compound, "isoöctane." It is produced synthetically for airplane fuel and is used as a standard substance in measuring the anti-knock properties of gasolines. The third formula is that of a highly compact structure. In normal octane the terminal carbon atoms are sometimes designated as primary, while the six central ones are secondary. In "isoöctane" there are five primary carbon atoms, one secondary, one tertiary, and one "neo" or quarternary carbon. In the third structure there are six primary carbon atoms and two "neo" carbons.

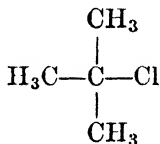
Replacement of hydrogen atoms by various means does not take place with equal ease in all positions. Hydrogen on a tertiary carbon atom for example reacts with dilute nitric acid at high temperature, whereas other hydrogen atoms are resistant under the same conditions. Derivatives containing neo carbon atoms (those attached to four other carbon atoms) show interesting and peculiar behavior.

The determination of the structure of an unknown hydrocarbon (isolated for example from petroleum) depends for the most part on comparison with a synthetic product, the structure of which is established by its method of synthesis.

Let us say a hydrocarbon (butane) with boiling point -11.7° C. has been obtained from petroleum but that its structure, whether straight or branched chain, is unknown. The straight chain hydrocarbon can be prepared for comparison by Wurtz

synthesis from $\text{CH}_3\text{CH}_2\text{Cl}$, but is found to boil at -0.55° . It must have the straight chain structure because of its method of formation. The hydrocarbon boiling at -11.7° therefore must have the branched chain. (This can also be proved by independent means.)

The octanes pictured above can all be synthesized by methods which settle the question of their structures. It would be premature to discuss these methods in detail because they involve unfamiliar compounds and reactions. Normal octane, however, can be prepared by Wurtz synthesis from $\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{Cl}$, but the other octanes are not obtained by this means. The third octane pictured can be prepared by a modification of the Wurtz synthesis starting with the substance:



Gradation of Properties. The series of similar hydrocarbons, of which the simplest is methane, is known as a *homologous series*. Each member after methane has in its molecular formula one carbon and two hydrogen atoms (CH_2) more than the preceding member. The molecular formulas of the whole series may be represented by a type formula $\text{C}_n\text{H}_{2n+2}$. Hydrocarbons with this type formula are called *saturated hydrocarbons*. The significance of this term will become more apparent after a study of Chapter IV.

The relationships between the melting points, boiling points and specific gravities of some of the members of the methane series are shown in the accompany table. It will be seen that all of these "physical constants" are higher for the substances with higher molecular weights. These hydrocarbons are almost insoluble in water, and the solubility decreases with higher molecular weight. These are important facts and apply not only to the hydrocarbons, but to all the classes of substances which we shall study, such as alcohols, acids, etc. In the case of any two homologous substances, it can be fairly safely predicted that the one with

the higher molecular weight (especially if it is considerably higher) will have the higher melting point, boiling point, specific gravity, and lower solubility in water. There are also other less important physical properties which show a similar gradation.

HYDROCARBONS OF THE METHANE SERIES

Name	Formula	Melting Point °	Boiling Point °	Density 20/4
Methane	CH_4	-182.5	-161.4	.415 (liq. -164°)
Ethane	C_2H_6	-183.2	-89	.446 (liq. 0°)
Propane	C_3H_8	-187.7	-42.1	.5007
Butane	C_4H_{10}	-138.3	-0.5	.5787
2-Methylpropane ...	C_4H_{10}	-159.4	-11.7	.5572
n-Pentane	C_5H_{12}	-129.7	36.0	.6262
2-Methylbutane	$\text{CH}_3\text{CH}_2\text{CH}(\text{CH}_3)_2$	-160.6	27.9	.6197
2,2-Dimethylpropane ..	$\text{C}(\text{CH}_3)_4$	-16.8	9.6	.5904
n-Hexane	C_6H_{14}	-95.4	68.6	.6594
3-Methylpentane	$\text{CH}_3\text{CH}(\text{C}_2\text{H}_5)_2$	-118.0	63.2	.6644
2-Methylpentane	$\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}(\text{CH}_3)_2$	-154.0	60.3	.6532
2,3-Dimethylbutane ...	$(\text{CH}_3)_2\text{CH}-\text{CH}(\text{CH}_3)_2$	-128.3	58.0	.6617
2,2-Dimethylbutane ..	$\text{CH}_3\text{CH}_2\text{C}(\text{CH}_3)_3$	-100.0	49.7	.6492
Heptane*	C_7H_{16}	-90.6	98.4	.6838
Octane	C_8H_{18}	-56.8	125.6	.7028
Nonane	C_9H_{20}	-53.7	150.7	.7181
Decane	$\text{C}_{10}\text{H}_{22}$	-29.7	174.0	.7299
Undecane	$\text{C}_{11}\text{H}_{24}$	-25.6	195.8	.7403
Dodecane	$\text{C}_{12}\text{H}_{26}$	-9.6	216.3	.7488
Tridecane	$\text{C}_{13}\text{H}_{28}$	-6.2	236.5	.7567
Tetradecane	$\text{C}_{14}\text{H}_{30}$	5.5	252.5	.774 (at M.P.)
Pentadecane	$\text{C}_{15}\text{H}_{32}$	10	270.5	.776 "
Hexadecane	$\text{C}_{16}\text{H}_{34}$	18	287.5	.775 "
Heptadecane	$\text{C}_{17}\text{H}_{36}$	22.5	303	.777 "
Octadecane	$\text{C}_{18}\text{H}_{38}$	28	317	.777 "
Nonadecane	$\text{C}_{19}\text{H}_{40}$	32	330	.777 "
Eicosane	$\text{C}_{20}\text{H}_{42}$	36.7	205†	.778 "
Heneicosane	$\text{C}_{21}\text{H}_{44}$	40.4	215†	.778 "
Docosane	$\text{C}_{22}\text{H}_{46}$	44.4	224.5†	.778 "
Tricosane	$\text{C}_{23}\text{H}_{48}$	47.7	234†	.778 "
Tetracosane	$\text{C}_{24}\text{H}_{50}$	51.1	243†	.779 "
Heptacosane	$\text{C}_{27}\text{H}_{56}$	59.5	270†	.780 "
Hentriacontane	$\text{C}_{31}\text{H}_{64}$	68.1	302†	.781 "
Dotriacontane	$\text{C}_{32}\text{H}_{66}$	70.5	310†	—
Pentatriacontane	$\text{C}_{35}\text{H}_{72}$	74.7	331†	.782

* From this point on only one isomer of each kind is listed.

† B.P. at 15 mm. pressure.

Naming of Paraffin Hydrocarbons. Some compounds have more than one name in common use, and simpler compounds, methane, ethane, propane, and butane are given arbitrary names which of themselves do not designate structure. As noted in the accompanying table (p. 21), the names of some of the hydrocarbons are derived from the Greek roots indicating the number of carbon atoms present.

Certain parts of molecules often do not change during various reactions and in all naming systems such groups of atoms or radicals are designated by special names: CH_3 , *methyl*; C_2H_5 , *ethyl*; $\text{CH}_3\text{—CH}_2\text{—CH}_2\text{—}$, *propyl*; $(\text{CH}_3)_2\text{CH—}$, *isopropyl*; etc. There are four butyl groups (C_4H_9) with different arrangements which will be mentioned later and eight *amyl* groups (C_5H_{11}). All of the groups mentioned so far are known collectively as *alkyl* groups. The higher alkyl groups are named hexyl, heptyl, etc., corresponding to the name of the hydrocarbon. CH_2 is designated the *methylene* (methene) group. Other radicals will be mentioned as occasion arises.

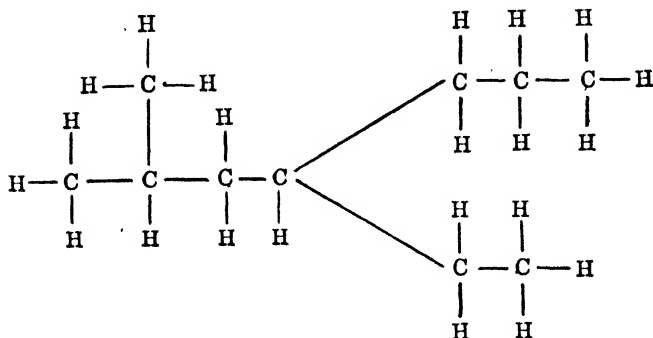
One system of naming which is often found in the chemical literature but which is not recommended for use involves designating the structure as a derivative of methane. A central carbon atom is chosen which is attached to as many groups as possible and is designated as the "methane" carbon, and the groups attached to this atom are named. According to this system, which is not used in simpler cases, ethane may be called methylmethane, propane is dimethylmethane, isobutane is trimethylmethane, etc. By a variation of this system the third octane pictured on p. 19 is hexamethylethane. This latter name is unambiguous and shorter than any other.

For the systematic naming of hydrocarbons (and other compounds) a system has been evolved from one originating in Geneva, Switzerland, in 1892, which is in general use. This represents the best thought of many individuals and has been modified in its details from time to time.

As applied to paraffin hydrocarbons, the first step in naming a formula or structure is to select the longest continuous chain of carbon atoms. If this chain is six carbons long the last name of the structure is *hexane*, if seven *heptane*, if eight *octane*, etc.

The second step is to number these carbon atoms consecutively, 1-6 or 1-8, starting at the end where more substituted groups are present. The third step is to indicate by number and name the substituted groups on the original chain.

Let us suppose that it is desired to name properly the hydrocarbon with the formula indicated below:



There is present a continuous chain of seven carbon atoms and the substance is therefore named as a substituted *heptanê*. After the carbon atoms are numbered it is apparent one methyl group is on the 2 position and an ethyl group is on the 4 position. The name is therefore *2-methyl-4-ethylheptane*. The first octane (I), p. 19, is called simply octane, or more explicitly normal octane. "Isooctane" (II) has a continuous chain of only five carbon atoms and is named 2,2,4-trimethylpentane. The third octane (III) has only four carbon atoms in a continuous chain and is named 2,2,3,3-tetramethylbutane.

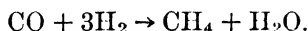
It is undesirable for the student to spend an excessive amount of time naming formulas for all sorts of "outlandish" hydrocarbons which no one has made or is likely to make. It is an interesting exercise but does not help materially in understanding chemical phenomena. The student should become sufficiently familiar with naming so that he can designate properly compounds which he may wish to consider, and to understand the names which may be used by writers on chemical subjects.

Preparation and Chemical Characteristics of Methane and Its Homologs. The principal source of the saturated hydro-

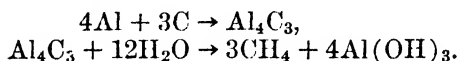
carbons is natural gas and petroleum. These naturally occurring mixtures of hydrocarbons will be discussed later in this chapter. Because these hydrocarbons are available in very large quantities and at a very low cost, there was little interest in their synthesis until recent years when it was discovered that certain hydrocarbons could be caused to join together to form valuable saturated compounds of higher molecular weight. These hydrocarbons are superior as a fuel for internal combustion engines and will be mentioned in connection with the discussion of petroleum. Saturated hydrocarbons have also been isolated in small amounts from the waxy constituents of certain plants.

Methane, or marsh gas, CH_4 , is found, as the latter name suggests, bubbling from marshes where organic matter is decaying. It is produced by many bacteria during their growth. Natural gas is frequently composed mostly of methane and constitutes its most important source. Ordinarily, coal gas contains from 30 to 40 per cent methane, while carburetted water gas contains only a low percentage.

Methane is formed in appreciable amounts by direct combination of carbon and hydrogen at about 1200° . It may also be obtained by the reduction of oxides of carbon in the presence of finely divided nickel which acts as a catalyst. For carbon monoxide the equation is



It is also formed by the action of water on aluminum carbide. Aluminum carbide is formed when carbon and aluminum are heated together to bright-red heat.



For study in the laboratory, methane is most often made by heating sodium acetate with soda lime. This reaction will be studied later, as well as other reactions by which methane may be prepared, which we are not ready to discuss because they involve unfamiliar substances.

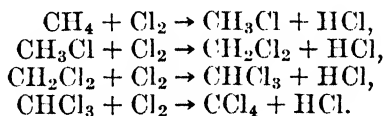
Homologs of methane. Homologs of methane may be prepared by methods analogous to those mentioned for methane. In

addition they may be prepared by the Wurtz synthesis and in several other ways which will be discussed in connection with the reactions of the specific compounds used in their preparation.

Chemical Characteristics of Saturated Hydrocarbons. Since methane is the first member of a family of closely related compounds much that will be said regarding it is true also of the other members of the family. These hydrocarbons in general are noted for their inertness and the name *paraffin* comes from *parvum affinis* (Latin) meaning "little affinity." Saturated hydrocarbons are frequently called *paraffin hydrocarbons*.

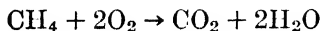
Methane gas may be allowed to come in contact with numerous reactive reagents, concentrated sulfuric acid, concentrated nitric acid, concentrated alkali, acid or alkaline permanganate, molten metallic sodium, etc., without being affected.

Reactions with Halogens. Fluorine, chlorine, and bromine are exceptional reagents in this regard because they all attack methane and its homologs. Fluorine (which is an uncommon reagent) reacts readily, producing carbon and hydrogen fluoride. Chlorine reacts similarly in bright light, but in diffuse light and at low temperature a stepwise replacement of hydrogen by chlorine takes place as indicated by the equations:



Bromine reacts less readily. Iodine fails to react.

High Temperature Reactions. The inertness of methane (and other saturated hydrocarbons) can readily be exaggerated, because it is only at low temperature that it remains unaffected by reagents. The most striking example of reactivity at high temperature is with oxygen. Powerful oxidizing agents fail to affect methane at ordinary temperatures, but if oxygen and methane are mixed and ignited with a spark they react explosively. In an excess of oxygen or air each volume of methane uses up two volumes of oxygen and yields one volume of carbon dioxide, and two volumes of water vapor.



In a diminished supply of oxygen, carbon monoxide and traces of other intermediate products are produced.

Methane and particularly its homologs will react readily with chlorine and bromine at high temperatures (400°) to produce halogenated hydrocarbons (p. 32). They will also react with nitric acid (420°) to give nitroparaffins (p. 214).

When heated with steam (800° - 1000°) in the presence of catalysts, methane (natural gas) yields carbon monoxide (1 mole) and hydrogen (3 moles). This constitutes a source of industrial hydrogen.

Even in the absence of reagents, methane undergoes reactions at high temperature (*e.g.*, 800°), due to the tendency of the methane molecules to fall apart, producing fragments which may reunite in various ways. Ethane, C_2H_6 , ethylene, C_2H_4 , acetylene, C_2H_2 , and benzene, C_6H_6 , are among the hydrocarbons which may be formed from methane by the action of heat alone. Hydrogen is also produced industrially by passing natural gas (methane) over brick at 1000° - 1100° or over a catalyst at lower temperatures.

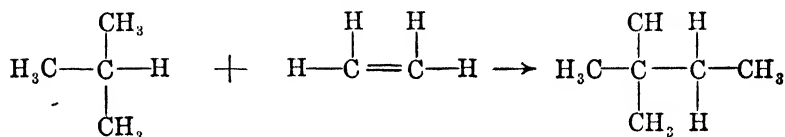
Cracking, Dehydrogenation, Alkylation, and Cyclization of Higher Hydrocarbons. When higher paraffin hydrocarbons are subjected to the action of heat in the presence or absence of catalysts numerous reactions occur. We are not yet prepared to discuss the various products in detail, but will indicate by formulas some of the transformations which occur. Many of the compounds involved in these transformations are unsaturated hydrocarbons which are not members of the paraffin series, and which are to be discussed in Chapter IV. After that chapter has been studied a re-reading of this material will have added meaning.

By use of catalysts such as chromium oxide and alumina, two and in some cases four or more atoms of hydrogen may be removed from saturated hydrocarbons. The resulting *unsaturated* hydrocarbons are reactive in distinction to the saturated hydrocarbons which are relatively inert.

Similar types of unsaturated hydrocarbons are produced by

the simple breakdown of saturated hydrocarbons. Consideration of their formulas will show that no saturated hydrocarbon can break down to yield *two* saturated hydrocarbons; one of the two must lack sufficient hydrogen to be a saturated hydrocarbon. The unsaturated hydrocarbons produced by these two methods can be used as starting materials for the production of a multitude of organic chemicals as will be made clear later.

In the reaction chamber itself where they are formed at elevated temperatures and pressures the "unsaturates" undergo three reactions of importance. (1) They may "alkylate" a saturated hydrocarbon as exemplified by the interaction between ethylene, C_2H_4 , and isobutane:



(2) They may polymerize (p. 62), yielding more complex hydrocarbons. (3) They may "cyclize," that is produce ring structures (p. 384). These reactions are very important in connection with the manufacture of high-grade gasoline.

Petroleum

Although petroleum has been known since antiquity it wasn't until August 27, 1859, that the first oil well in the United States began producing petroleum (crude oil). This well was 66 feet deep and produced 15 barrels of oil per day; during World War II, oil production was over 5,000,000 barrels per day from wells some of which were more than 10,000 feet in depth. This tremendous expansion of the petroleum industry has been concomitant with correspondingly great technological advances. Petroleum, of course, has not been the basis of all the technological advance of modern civilization but it has contributed a great deal. Originally, petroleum was used as a fuel (for heating) and an illuminate (kerosene). It is still used as a fuel for heating but it is now more important as the fuel which has made possible

the internal combustion engine. In recent years, however, petroleum and the paraffin hydrocarbons contained therein have become an important source for practically all types of starting materials used in the whole field of organic chemistry, and its importance in this respect will doubtless increase as time goes on. Petroleum derivatives, to mention a few, include medicinals, fertilizers, insecticides, dyes, alcohols, plastics, plant growth stimulators and fruit ripeners. It should also be noted that modern warfare could not be waged if it were not for petroleum.

It has already been mentioned that petroleum is a complex mixture of hydrocarbons and is the source of many individual compounds. The nature of these compounds vary within rather wide limits, depending upon the origin of the petroleum. Certain types of petroleum, notably that from the Pennsylvania fields, are made up largely of paraffin hydrocarbons, containing up to about thirty-five carbon atoms. Some of the products obtained directly by distillation of such petroleum are listed below.

PETROLEUM PRODUCTS

	Density (Approx.)	Boiling Point ° (Approx.)	Uses
Natural gas		below 0	Fuel, syntheses and carbon black
Liquified gases...	.60	0	Fuel and syntheses
Petroleum ether...	.63	20-60	Solvents and syntheses
Light naphtha....	.65	40-90	Solvents
Gasoline74	40-205	Fuel (engines)
Kerosene80	175-325	Fuel (Diesel and jet engines) and cracking
Gas oil86	above 275	Fuel and cracking
Lubricating oils..	.91	above 300	Lubricants
Residium			Vaseline, paraffin wax, road oils, asphalt, coke

In addition to saturated hydrocarbons, petroleum contains lesser amounts of cyclic (p. 384) and aromatic (p. 406) hydrocarbons and oxygen, sulfur and nitrogen compounds. These latter compounds are, in general, complex in nature as they occur in the petroleum but tend to break down into smaller molecules during the distillation of the crude oil. The sulfur compounds

are especially undesirable in gasoline because they decrease the effectiveness of tetraethyllead (p. 44), have an unpleasant odor and are often corrosive. These and other objectionable compounds are removed by refining the gasoline. There are no unsaturated hydrocarbons in crude oil but they are formed during the processing of the petroleum.

Progress in petroleum technology and research has been very rapid in recent years. A decade or two ago relatively little was known regarding the potentialities of petroleum chemistry and its utilization involved principally separation by distillation of the various useful products (mixtures). Today, however, petroleum constituents are altered so that the final marketed products may have little relation chemically to the constituents originally present in the oil. Among the more important treatments applied are thermal and catalytic cracking. So many variations in processes (as well as variations in crude oil) are current that it is impossible to give more than an elementary idea regarding some of the practices. Cracking involves heat treatment either with or without a catalyst (aluminum oxide is often used) and results in the breaking down of larger molecules into smaller, as well as other structural changes. Accompanying the changes in molecular size are changes in chemical characteristics (p. 26). Much of the research in petroleum chemistry has been directed to the production of more gasoline and gasoline of higher "anti-knock" value. The amount of gasoline obtainable from crude oil has been more than doubled and at the same time its quality for use in high-compression motors has been tremendously improved.

Petroleum is thought to originate in the remains of fish, molluscs, diatoms, etc., which have been deposited in ocean beds. The potential supply in America is certainly larger than was formerly supposed and some competent authorities believe that petroleum is being formed on earth more rapidly than it is being used.

Anti-Knock Properties of Hydrocarbons—Octane Numbers. High-compression engines demand the use of gasoline of high anti-knock quality, and are highly efficient when properly

fueled. Extensive research has shown that three types of hydrocarbons may improve the anti-knock qualities of a gasoline: (1) paraffin hydrocarbons with "compact" structures (not straight chain types); (2) unsaturated hydrocarbons; (3) cyclic (including aromatic) hydrocarbons.

The "octane number" of a gasoline is based upon a comparison of its anti-knock properties with various blends of "isoöctane" and normal (straight chain) heptane. "Isoöctane" has excellent anti-knock properties, and *n*-heptane is very poor in this respect. A 70 octane gasoline is equivalent to a mixture of 70 per cent "isoöctane" and 30 per cent *n*-heptane. "Isoöctane" itself has an octane rating of 100. During World War II, catalytic cracking was developed to such a degree that 100 octane gasolines were produced. Gasolines of lower anti-knock value can be improved markedly (some are more susceptible than others) by introducing tetraethyl lead (p. 44). Aviation gasoline is a blend of several types of gasoline plus a number of different additives.

Gasolines with octane numbers of 100 or better will be available for use in automobiles in the course of a few years and the use of higher compression ratios will lead to increased efficiency and fuel economy.

PROBLEMS

1. Write out the skeleton formulas (omitting hydrogen symbols) for all the octanes and convince yourself that eighteen and only eighteen structures are possible.

2. Work out all the possible structures corresponding to the molecular formula, $C_6H_{13}Cl$, and give each a systematic name.

3. Calculate the percentage of carbon and hydrogen in the following: (1) CH_4 , (2) C_2H_6 , (3) $C_{30}H_{62}$, and (4) $C_{31}H_{64}$. Would the first two be easily distinguished by analysis? What about the third and fourth? Could the third and fourth hydrocarbons be distinguished easily by some other means?

4. List the following gases in the order of their density: C_2H_6 , CO , NH_3 , CH_4 , H_2O .

5. How much carbon dioxide would be produced (expressed in cc.) by the burning of (a) 20 cc. of pure propane, (b) 20 cc. of a mixture of equal quantities of propane and ethane?

6. If *n* equals the number of moles of water produced by the burning of one mole of a compound *x*, how many hydrogen atoms are present per molecule of *x*?

7. Suppose 15 cc. of a mixture of methane and ethane yield on combustion 20 cc. of CO_2 , in what proportion were the two gases in the original mixture?

8. Show by equations how the following hydrocarbons could be built up from halogen substitution products: (a) normal butane, (b) isobutane, (c) 3-methylpentane, (d) normal pentane.

9. What is the total number of outer shell electrons in a molecule of (1) methane, (2) butane, (3) methyl bromide, (4) ethyl iodide, (5) ammonia, (6) water? Are there any molecules you can think of that have an uneven number? If so, what distinctive properties do they possess?

10. Considering the existence of two kinds of hydrogen aside from the ordinary variety (*c.g.*, deuterium D and tritium T) work out the total number of possible methanes.

11. It is possible by catalytic oxidation in the vapor phase to oxidize a hydrocarbon $\text{C}_{10}\text{H}_{22}$ to an acid $\text{C}_{10}\text{H}_{20}\text{O}_2$. What relationship should exist between the volumes of oxygen and hydrocarbon (vapor) used in order to bring this about?

CHAPTER III

HALOGEN SUBSTITUTION PRODUCTS OF SATURATED HYDROCARBONS

The reaction of chlorine with methane has been mentioned (p. 25) but little information regarding the reaction or the products formed from any of the paraffin hydrocarbons has been given.

Control of Chlorination. The series of reactions resulting in a stepwise substitution of one after another of the hydrogen atoms in methane by chlorine presents an interesting case inasmuch as the product of the initial reaction methyl chloride, CH_3Cl , is more readily attacked by chlorine than is methane itself. Hence if equimolecular proportions of methane and chlorine are mixed and caused to react, the principal product will not be methyl chloride, CH_3Cl , but is more likely to be carbon tetrachloride, CCl_4 , since the small amount of methyl chloride formed in the first stages of the reaction is attacked by the unused chlorine more readily than is the methane, even though the latter is in higher concentration.

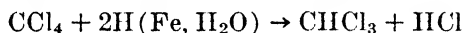
By using a high concentration of methane, perhaps twenty times that of the chlorine, the situation is changed so that there is a greatly increased probability of the chlorine molecules colliding with methane molecules instead of methyl chloride molecules; as a result, the methane which is attacked is converted largely to methyl chloride, and secondary products, CH_2Cl_2 , CHCl_3 and CCl_4 , are not formed to a large extent.

With the higher homologs of methane there are produced not only the expected poly chlorides but also all the theoretically possible monochloro compounds. The multiplicity of products obtained with even the simple hydrocarbons has inhibited the commercial development of chlorination as a means of organic chloride synthesis. The pentane cut of natural gasoline con-

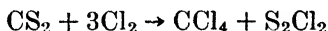
taining about equal amounts of *n*-pentane and isopentane is, however, chlorinated industrially in the dark at 200° to give a mixture of chlorides. These chlorides are not utilized as such but are hydrolyzed to alcohols (p. 83), which are of greater economic value. The chlorination of paraffin yields important products (parafflow) which are used to prevent crystallization of wax out of lubricating oils when they are chilled.

Indirect Methods of Preparation of Halides. The usual methods for preparing organic halides is *not* by direct halogenation of saturated hydrocarbons. A method commonly used for the preparation of alkyl bromides and iodides consists in the treatment of the appropriate alcohol with constant-boiling hydrobromic or hydriodic acid (p. 85). Hydrochloric acid is less reactive and if it is used, zinc chloride must be used as an activator. Phosphorus polyhalides may also be used to convert alcohols to halides. The hydrogen halides may also be added chemically to unsaturated compounds, usually in the presence of a catalyst, to yield alkyl halides (p. 52).

Chloroform (CHCl_3) may be prepared from ethyl alcohol or acetone by the Haloform Reaction to be discussed later (p. 118) or by the reduction of carbon tetrachloride.



Carbon tetrachloride is prepared commercially for the most part by the chlorination of carbon disulfide in the presence of a catalyst or halogen carrier (usually antimony (V)¹-chloride, aluminum chloride or ferric chloride).

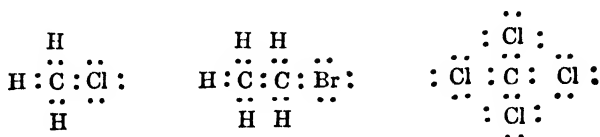


Carbon disulfide in turn is made by the direct union of the elements when sulfur vapor is passed over hot coke in an electric furnace.

It is of interest to observe that compounds are by no means always prepared in accordance with the most obvious and direct method.

¹ The Roman numeral is used to denote the valence number of the metal ion.

Character of Linkage in Halides. It is important to note that in methyl chloride, CH_3Cl , ethyl bromide, $\text{C}_2\text{H}_5\text{Br}$, carbon tetrachloride, CCl_4 , and all other similar halides the mode of linkage between carbon and halogen is the same, namely through a covalent bond of shared electrons. The compounds mentioned may be represented as follows:



The electron shells of the carbon atoms and the halogen atoms are completed through pairs of electrons which are jointly held.

From our previous discussion it is clear that these compounds cannot undergo ionization in the ordinary sense, because while the "makings" of a chloride ion is present in the methyl chloride molecule, it cannot separate without leaving behind the extremely

unstable structure $\text{H} : \ddot{\text{C}} : \text{H}$ in which carbon has only a sextet of

electrons. In all typical cases of salts, etc., where ionization is known to take place, the two ions formed have *completed* rather than *uncompleted* electron shells.

There is evidence that in methyl chloride, as well as in other halides, the halogen kernel has more of a pull upon the electrons than the carbon, and there is said to be electron displacement toward the chlorine. That there is no ionization is clear not only from the discussion above but also from the experimental fact that such compounds do not show ionic conduction of electric currents, and do not give tests for halide ions, for example with silver nitrate.

The question naturally arises as to how these compounds react and how halide ions may be produced from them. We have already mentioned the Wurtz synthesis in which sodium chloride is a product and have commented on the frequent ease with which sodium chloride is formed, when compounds containing the two elements sodium and chlorine are brought together.

The best interpretation of the Wurtz reaction (which ordinarily requires heat) is that, for example, the methyl chloride *molecules* actually collide with sodium atoms, and that as a result of these collisions chloride ions *are formed* simultaneously with the formation of sodium ions. We may think of the chlorine kernel as being "greedy" for electrons. In the methyl chloride molecule it can only be satisfied by sharing one pair of electrons with carbon. When in this combination it comes in contact by collision with a potential source of free electrons (sodium atoms) it leaves its combination with carbon, accepts electrons from sodium and becomes a chloride ion. This leaves behind an un-

$$\begin{array}{c} \text{H} \\ \vdots \\ \text{H} \end{array} \text{C} \cdot$$

stable structure (free radical) which must stabilize it-

$$\begin{array}{c} \text{H} \\ \vdots \\ \text{H} \end{array} \text{C} \cdot$$

self in some way. Actually when many such structures are formed simultaneously they can readily stabilize themselves by joining in pairs with another of like kind to yield ethane, C_2H_6 . It should be noted that the formation of the chloride ion takes place through the action of a powerful reagent, and that the reaction is not ionic because the presence of the ion did not precede the reaction. (In ionic reactions the ions are preformed in solution and are the cause rather than the result of the reaction.) The above may be called an *ionogenic* reaction.

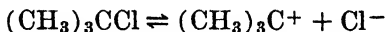
Vapor phase reactions between alkyl halides and metallic sodium (vapor) at about 300° have been studied extensively (Polanyi) and the results are in line with the above interpretation. As is usually the case with gaseous (or other) reactions only a fraction of the collisions results in reaction. The differences in the reactivity of the common halides are shown by the following numbers of collisions between the halide molecule and sodium necessary (statistically) to yield a halide ion:

Ethyl iodide	5
Ethyl bromide	70
Ethyl chloride	1000

There are many other reagents besides metallic sodium or other strongly metallic elements which will also cause, by interaction, the *production* of chloride ions from methyl chloride. By heating methyl chloride with sodium hydroxide solution a result

somewhat similar to the above takes place. The actual detailed mechanisms of even the simplest chemical reactions are often complex and unknown and in this discussion we are concerned only with certain elementary and fundamental conceptions. No one knows precisely all the details of the reaction under consideration. It is clear, however, that methyl chloride of itself does not give rise to chloride ions, but that through the agency of sodium hydroxide solution, chloride ions are slowly formed. The reaction is most simply pictured as involving a collision between hydroxyl *ions* (other bases than sodium hydroxide will function) and methyl chloride *molecules*. The chlorine kernel is again "greedy" for electrons and in this case is able to capture an electron and become a chloride ion, leaving the two fragments methyl and hydroxyl to join together forming CH_3OH . Again this is not an ionic reaction (ionic interchange), but involves the production of one ion (chloride) and one molecule (CH_3OH), from another ion (hydroxyl) and another molecule (CH_3Cl). It may be termed a *semi-ionic* reaction since one of the two reactants is an ion. The reaction is a very general one and barring side reactions which may seriously complicate the picture in the case of higher homologs, an ion which has less affinity for electrons than the chloride ion can react with methyl chloride, or other alkyl halide, to yield chloride ion and the corresponding alkyl compound. Many such cases will be noted in our further study.

When the hydrogens of methyl chloride have been replaced with alkyl groups, as in the case of *tertiary* butyl chloride, $(\text{CH}_3)_3\text{CCl}$, there is good evidence that at least some ionization of the chloride to a carbonium ion and a chloride ion takes place before collision with an ion.



This unusual type of behavior will be discussed in a later chapter (p. 532).

The Fundamental Character of the Halides. Since the halides which we have been discussing are, in general, incapable because of their structure of undergoing ionization, and fur-

thermore give no evidence of ionization, they cannot be regarded as salts. Furthermore, they are relatively highly volatile compounds with little tendency to dissolve in water and in these respects differ markedly from salts.

From their general relationships it becomes clear that the halides which have been under consideration are not only analogous, but also similar to halides of phosphorus, sulfur, and other non-metallic elements (carbon is definitely non-metallic). Though the point is not often stressed in inorganic text books these compounds may best be regarded as mixed acid anhydrides; they react with water to yield two different acids. Phosphorus trichloride is the mixed anhydride of phosphorous and hydrochloric acids and yields these two acids upon reacting with water. Phosphorus pentachloride is the mixed anhydride of phosphoric and hydrochloric acid. Sulfuryl chloride, SO_2Cl_2 , a slightly different type, is the mixed anhydride of sulfuric and hydrochloric acids. All of these compounds are like the simple anhydrides, SO_3 , SO_2 , CO_2 , P_2O_5 , etc., in that they fail themselves to undergo ionization, are volatile, and react with water to form acids.

Carbon tetrachloride, CCl_4 , like phosphorus halides, for example, reacts (difficultly) with water to yield two different acids, carbonic and hydrochloric, and is therefore a mixed acid anhydride. The alkyl halides are also mixed acidic anhydrides as will be made clear in a later chapter.

Relative Reactivity of Different Halides. Alkyl iodides are definitely more reactive than the corresponding bromides which, in turn, are more reactive than the chlorides. This is illustrated by the fact that when methyl iodide or ethyl iodide is introduced into an alcoholic solution of silver nitrate, silver iodide is precipitated immediately, while the corresponding bromine and chlorine compounds do not cause the immediate precipitation of silver halides in this way. The reaction between alkyl iodides and silver nitrate has been studied, and, although it is a rapid reaction, there are indications that it involves interaction between molecules rather than an interchange of ions. While the bromine and chlorine derivatives do not react with silver

nitrate to cause immediate precipitation, they react on heating. When heated they may also react by double decomposition with other salts. We will have occasion later to mention the reactions which these substances undergo with potassium cyanide, potassium nitrite, etc. Iodides and bromides are often used in laboratory operations, but industrially, where expense of materials is a more important item, the chlorides are preferred.

The position occupied by a halogen atom has a determining influence on its reactivity. Halogen atoms which are attached to carbon which is attached directly to only one other carbon (*primary* halides) are often more reactive than when the carbon is attached to two or three other carbons. Halides of the latter type are known as *secondary* and *tertiary* halides respectively. Reactions differ, however, and generalizations should not be made too definite. In many cases the reactions take different paths depending on the structure of the halide (Whitmore, p. 70, *et. seq.*). Halides of the higher paraffins usually are less reactive than the corresponding lower halides.

Physical Properties and Uses. A number of halogen derivatives of paraffin hydrocarbons are listed in the accompanying tables on page 39.

Halogen substitution products of the hydrocarbons as a rule are very slightly soluble in water. The derivatives of the higher hydrocarbons and those containing several atoms of the halogen are more nearly insoluble. Some of the above compounds are of considerable importance. *Methyl chloride* and *methyl bromide* (p. 39) are gases and are not often used in the laboratory. Methyl chloride has been used, however, as a refrigerant in electric refrigerators, while methyl bromide is used as an insecticide. *Methyl iodide* is a low boiling liquid and is often used in spite of the expensiveness which is common to all iodine compounds. *Ethyl chloride* is a gas which is liquefied and sold as a freezing agent for the production of local anesthesia. Like other liquids it takes up heat when it vaporizes, and the high volatility facilitates obtaining a low temperature. The use of ethyl chloride for this purpose is not based upon any peculiar properties, except that it is chemically inert and does not react with

ALKYL CHLORIDES

Boiling Point °

Methyl chloride	CH_3Cl	-24.2
Ethyl chloride	$\text{C}_2\text{H}_5\text{Cl}$	12.2
<i>n</i> -Propyl chloride	$\text{CH}_3\text{CH}_2\text{CH}_2\text{Cl}$	46.5
Isopropyl chloride	$(\text{CH}_3)_2\text{CHCl}$	36.5
<i>n</i> -Butyl chloride	$\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{Cl}$	77.5
Isobutyl chloride	$(\text{CH}_3)_2\text{CHCH}_2\text{Cl}$	68.5
<i>Sec.</i> butyl chloride	$\text{C}_2\text{H}_5\text{CHClCH}_3$	68
<i>Tert.</i> butyl chloride	$(\text{CH}_3)_3\text{CCl}$	51.5
<i>n</i> -Amyl chloride (there are eight isomers)	$\text{CH}_3(\text{CH}_2)_4\text{CH}_2\text{Cl}$	108
<i>n</i> -Hexyl chloride	$\text{CH}_3(\text{CH}_2)_5\text{CH}_2\text{Cl}$	133
<i>n</i> -Heptyl chloride	$\text{CH}_3(\text{CH}_2)_6\text{CH}_2\text{Cl}$	159
<i>n</i> -Octyl chloride	$\text{CH}_3(\text{CH}_2)_7\text{CH}_2\text{Cl}$	185

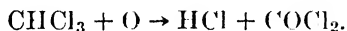
HALOGEN DERIVATIVES

Boiling Point ° Density

Methyl fluoride, CH_3F	- 78	—
Methyl chloride, CH_3Cl	- 24.2	.920 (18°)
Methyl bromide, CH_3Br	4.5	1.73 (0°)
Methyl iodide, CH_3I	42.5	2.285 (15°)
Ethyl fluoride, $\text{C}_2\text{H}_5\text{F}$	- 37.7	—
Ethyl chloride, $\text{C}_2\text{H}_5\text{Cl}$	12.2	.921 (0°)
Ethyl bromide, $\text{C}_2\text{H}_5\text{Br}$	39	1.45 (15°)
Ethyl iodide, $\text{C}_2\text{H}_5\text{I}$	72.3	1.94 (15°)
<i>n</i> -Propyl fluoride, $\text{C}_3\text{H}_7\text{F}$	below	—
<i>n</i> -Propyl bromide, $\text{C}_3\text{H}_7\text{Br}$	71.5	1.362 (16°)
<i>n</i> -Propyl iodide, $\text{C}_3\text{H}_7\text{I}$	102.4	1.747 (16°)
Ethylene dichloride, $\text{C}_2\text{H}_4\text{Cl}_2$	84	1.280 (0°)
Ethylene dibromide, $\text{C}_2\text{H}_4\text{Br}_2$	131.6	2.189 (15°)
Ethylidene dichloride, CH_3CHCl_2	57.3	1.178 (15°)
Ethylidene dibromide, CH_3CHBr_2	112.5	2.1 (15°)
Methylene dichloride, CH_2Cl_2	42	1.377 (15°)
Methylene dibromide, CH_2Br_2	98.5	2.498 (15°)
Methylene di-iodide, CH_2I_2	180	3.332 (15°)
Fluoroform, CHF_3	20	2.5 (approx.)
Chloroform, CHCl_3	62	1.499 (15°)
Bromoform, CHBr_3	151.2	2.904 (15°)
Iodoform, CHI_3	119	4.08 (17°)
Carbon tetrachloride, CCl_4	76.7	1.584 (25°)
Dichlorodifluoromethane, CCl_2F_2	- 30	—
Carbon tetrabromide, CBr_4	189.5	3.42 (15°)
Carbon tetraiodide, CI_4	decomp.	4.32 (20°)
Hexachloroethane, C_2Cl_6 (m.p. 185°)	subl.	1.998 (29°)
Hexabromoethane, C_2Br_6	210	—
Tetrafluoroethylene, CF_2CF_2	- 76.3	—

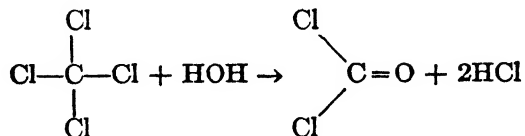
the tissues. Large quantities of ethyl chloride are used in the manufacture of tetraethyllead. *Ethyl bromide* is a low boiling liquid and is cheaper than *ethyl iodide*. Both compounds, however, are used in the preparation of Grignard reagents, etc.

Chloroform has been used extensively as an anesthetic. It is not used so extensively as formerly for this purpose, but has some advantages. It is characterized by the quickness with which it anesthetizes. In the presence of oxygen and light, chloroform undergoes decomposition into hydrogen chloride and phosgene (carbonyl chloride) which is poisonous.



Chloroform, U.S.P. (United States Pharmacopeia), containing a small amount of alcohol, and kept in appropriate containers, is safe as an anesthetic, as far as danger from phosgene is concerned. Chloroform is used in chemical laboratories as a solvent. It does not burn under ordinary conditions because it constitutes the next to the last step in the oxidation of methane with chlorine.

Carbon tetrachloride is similar to chloroform in most of its chemical properties and is used as a solvent. It does not burn and is used in *Pyrene* fire extinguishers. It is not suitable for use in large fires where people are likely to be trapped because in the presence of water at high temperature it is partially hydrolyzed to the poisonous phosgene gas.

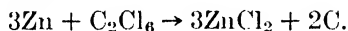


Carbon tetrachloride is mixed with gasoline to make non-flammable solvents for cleaning clothing, etc. If the percentage of the more expensive carbon tetrachloride is sufficiently high, the mixture will not burn.

Iodoform, CHI_3 , the iodine compound corresponding to chloroform, can be prepared by reactions similar to those used in the preparation of chloroform. It has been used extensively in the past and is used to some extent now as an antiseptic. Its

antiseptic properties are thought to be due to the fact that it decomposes readily with the liberation of iodine which is known to have strong antiseptic properties.

Ethylene dichloride is an excellent extraction solvent and dehydrating agent. Both ethylene dichloride and the dibromide are used in Ethyl fluid for anti-knock gasoline. *Hexachloroethane* is used in smoke candles and smoke pots by the U. S. Army under the name of "HC-Mixture." The mixture consists of 36 per cent zinc dust, 44 per cent hexachloroethane, 10 per cent ammonium perchlorate and 10 per cent ammonium chloride. A suitable igniter will start an exothermic reaction between the zinc dust and the organic halide.



Sufficient heat is generated to volatilize the zinc chloride and produce a dense smoke.

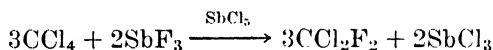
The existence of isomeric derivatives even among the halogen derivatives of the simpler paraffins should be noted. Thus the theory and the facts are in perfect accord with respect to the existence of two compounds $\text{C}_2\text{H}_4\text{Cl}_2$ (or $\text{C}_2\text{H}_4\text{Br}_2$), four compounds $\text{C}_3\text{H}_6\text{Cl}_2$ and five compounds $\text{C}_3\text{H}_5\text{Cl}_3$. Most of the polyhalogen derivatives of hydrocarbons with more than three carbon atoms are rare and unimportant. Mixed derivatives in which different halogens are present are difficult to make and with the exception of the chlorofluoromethanes which are used as refrigerants (p. 42) are of no great value. It is interesting scientifically to note, however, that over 75 halogen substitution products of ethane alone have been prepared.

Fluoro Compounds

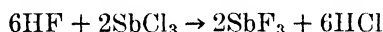
Fluorinated hydrocarbons are not readily obtained by use of the methods commonly employed for the production of any of the other alkyl halides. One of the reasons for the difficulties encountered in the preparation of the monofluoro derivatives is their marked instability. Polyfluorides in which two or more fluorine atoms are attached to the same carbon are, on the other hand, distinctly inert chemically. This effect is extended to

other halogens on the same or on adjacent carbon atoms. Because of their great stability and their low boiling points, the polychlorofluoromethanes and ethanes are widely used as refrigerant liquids and for air-conditioning units under the general name of "Freon." In addition to having satisfactory physical properties they are nontoxic, noncorrosive, noninflammable and nearly odorless. They are also used as the solvent and propellant in aerosol germicide and insecticide bombs.²

Dichlorodifluoromethane, (Freon-12) is prepared industrially by the replacement of two chlorine atoms of carbon tetrachloride by fluorine through the action of antimony (III) fluoride in the presence of an antimony (V) halide as a catalyst.



The antimony (III) fluoride is produced by the reaction between liquid hydrogen fluoride and antimony (III) chloride.



FLUORO COMPOUNDS

<i>Freons</i>			Boiling Point °
Monochlorodifluoromethane	(Freon-22)	CHClF_2	-40.8
Dichlorodifluoromethane	(Freon-12)	CCl_2F_2	-29.8
Dichloromonofluoromethane	(Freon-21)	CHCl_2F	8.9
Trichloromonofluoromethane	(Freon-11)	CCl_3F	23.7
Dichlorotetrafluoroethane	(Freon-119)	$\text{C}_2\text{Cl}_2\text{F}_4$	3.6
Trichlorotrifluoroethane	(Freon-113)	$\text{C}_2\text{Cl}_3\text{F}_3$	47.6

From Du Pont Products Index, E. I. Du Pont de Nemours and Co (Inc.), 1946, Wilmington 98, Delaware.

² The following analysis is typical of a germicide bomb (Sterel):

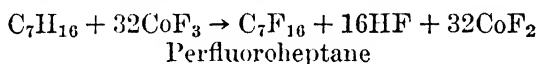
Active Ingredients:

Dipropylene Glycol	5%
Cetyltrimethylammonium Bromide	1%
Isopropyl Alcohol	9%

Inert Ingredients:

Mineral Oil	5%
Dichlorodifluoromethane	80%

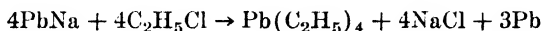
Fluorocarbons, C_nF_{2n+2} . During research associated with atomic fission appreciable technical and scientific information was obtained pertaining to compounds containing only fluorine and carbon. Two methods were developed for the production of these fluorocarbons. They can be prepared by direct fluorination of the corresponding hydrocarbon by gradually mixing the hydrocarbon vapor and fluorine, both diluted with nitrogen, in the presence of fine copper turnings coated with a thin layer of silver fluorides. The reaction takes place over a temperature range of 140° to 325° . The cobalt (III) fluoride process consists of the production of the trifluoride from cobalt (II) fluoride by treating CoF_2 with gaseous fluorine at 200° to 250° followed by vaporization of the hydrocarbon over the fluorinating agent at a graded temperature of 225° to 350° . With *n*-heptane the chemical reactions are:



Fluorocarbons are characterized by their extreme thermal stability and inertness towards even the most reactive chemical reagents. Because of these properties there will be a markedly increased interest in fluorine chemistry during the next few years. There is already available a new heat-resistant, chemically inert polytetrafluoroethylene, $(CF_2CF_2)_x$, plastic called Teflon. The abundance of fluorine on the earth's surface is comparable to that of carbon, nitrogen and chlorine.

Naming of Halide Derivatives. The simpler halides in which the alkyl radical has a common name are more often called simply *ethyl bromide*, *propyl iodide*, *secondary butyl chloride*, etc. If it is desired to name more complex derivatives the same system is used as with the hydrocarbons: (1) find the longest continuous carbon chain; (2) number the carbon atoms and designate the position of the substituents by these numbers. Because of the relative unimportance of halogen derivatives of higher paraffins, naming is seldom a problem.

Tetraethyllead (TEL), $\text{Pb}(\text{C}_2\text{H}_5)_4$. The most important use of ethyl chloride is in the manufacture of tetraethyllead. This organo-metallic compound is made by the reaction between ethyl chloride and a sodium-lead alloy at moderate temperatures and pressures.



One plant has an annual capacity of 30,000 tons of tetraethyllead.

Tetraethyllead is used to improve the anti-knock properties of gasoline. Formerly it was used only in special grades but now is used in over 88 per cent of all American gasolines. It is added in the form of Ethyl fluid consisting of approximately 63 per cent tetraethyllead, 26 per cent ethylene dibromide, 9 per cent ethylene dichloride and 2 per cent dye. If the dibromide is omitted the lead oxide formed in the cylinders, acting as a flux, removes the oxide coating of the spark points and eats them away. When the dibromide is used, lead bromide is formed, volatilizes and escapes into the exhaust. Thousands of tons of ethylene dibromide are used annually for this purpose. The amount of tetraethyllead used per gallon of gasoline varies from 0.75 to 3 ml. Aviation gasolines are more heavily leaded.

Tetraethyllead is very poisonous and its manufacture and use is attended by dangers unless properly safeguarded. Breathing the vapors or contact of the liquid with the skin may cause poisoning. In chemical properties, tetraethyllead is unlike the magnesium and zinc compounds (p. 147) in that it does not react with water.

PROBLEMS

1. Work out the structural formulas for all of the amyl chlorides, $\text{C}_5\text{H}_{11}\text{Cl}$, and assign to each a systematic name.
2. Write structural formulas for the following: (1) 1,2-dichloropropane, (2) 1-iodo-2,2-dibromopropane, (3) 1,2,3,4-tetrachloropentane, and (4) 1-chloro-2-methylbutane.
3. Taking into account the fact that in the laboratory we always deal with very large numbers of molecules which are not acted upon simultaneously, picture what substances may result from a Wurtz reaction in which methyl bromide and ethyl bromide together are treated with metallic sodium.
4. What butyl halides could be made to yield 2,2,4-trimethylpentane by Wurtz synthesis? What other hydrocarbon products would result? Name them.
5. How many hydrocarbons, C_8H_{18} , theoretically can be produced from the butyl chlorides by Wurtz synthesis?
6. To what general types mentioned in Chapter III, if any, do the following reactions belong: (1) $2\text{H}_2 + \text{O}_2 \rightarrow 2\text{H}_2\text{O}$, (2) $2\text{Na} + 2\text{H}_2\text{O} \rightarrow$

$2\text{NaOH} + \text{H}_2$, (3) $\text{AgNO}_3 + \text{HCl} \rightarrow \text{AgCl} + \text{HNO}_3$, and (4) $\text{Cl}_2 + \text{NaOH} \rightarrow \text{NaCl} + \text{NaOCl}$?

7. Alkyl fluorides are much less reactive than other alkyl halides. Is this an unexpected behavior in view of the reactivity of fluorine? Why?

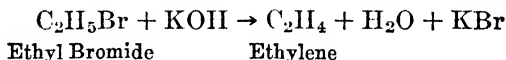
8. Starting with a lead atom with four external electrons, sodium, and ethyl chloride, picture electronically how a molecule of tetraethyllead may be formed. Note the similarity of the first step to the Wurtz synthesis.

CHAPTER IV

UNSATURATED HYDROCARBONS

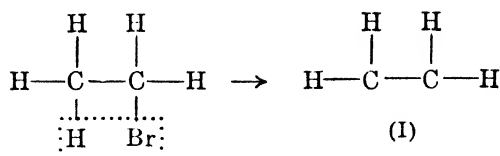
Ethylene Series (Alkenes, Olefins)

In the gaseous products which are formed by the cracking of petroleum there are likely to be present a number of compounds of similar chemical properties, with molecular formulas C_2H_4 , C_3H_6 , C_4H_8 , etc. These compounds, called alkenes, differ only slightly from the saturated hydrocarbons in physical properties but contrast sharply with them in chemical properties. The differences in chemical characteristics are not only in degree but also in the type of reaction. Bromine, for example, reacts with saturated hydrocarbons only at high temperatures or in the presence of actinic light while it reacts rapidly with alkenes at low temperatures and in the absence of light. The reaction with saturated hydrocarbons is a typical one of substitution but with alkenes the products can be accounted for only by assuming that the bromine has added on to the alkene. The unsaturated character of the alkenes is further indicated by the fact that they may be produced by a number of different reactions involving the removal of various elements from a molecule. An example of this type of reaction is the production of the gas, C_2H_4 , by the removal of the elements of H and Br from ethyl bromide using alcoholic potassium hydroxide.

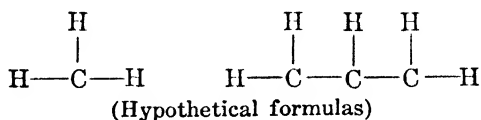


The type formula of an alkene is C_nH_{2n} .

Structure of Ethylene (Ethene), C_2H_4 . From a consideration of the one reaction cited we would give ethylene the following structure, which would be the simplest.



If (I) is a true picture there should be other compounds with carbon having a valence of three such as represented below:



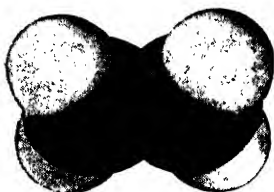
The fact that no one has ever been able to prepare compounds corresponding to the formulas CH_3 and C_3H_5 leads one to doubt the validity of formula (I) for ethylene. With rare and anomalous exceptions hydrocarbons always have *even numbers of hydrogen atoms* per molecule.

If we picture the above formula (I) taking into consideration the number of electrons in the atomic shells, we arrive at structure (II).



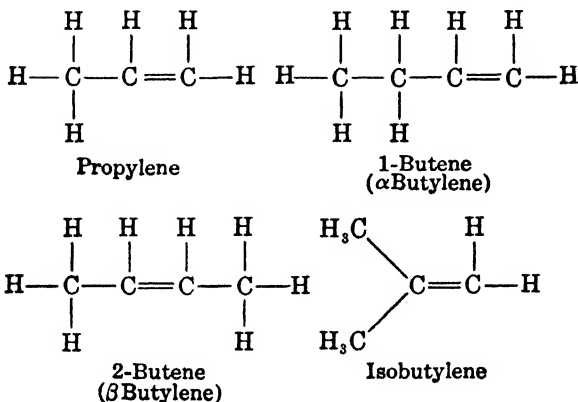
The total number of valence electrons must be 12; 4 for each carbon atom and 1 for each hydrogen atom. As pictured in (II) each carbon atom has seven electrons in its outer shell and we should expect this arrangement to be unstable. If the two lone electrons pictured above become paired the more stable arrangement (III) results in which each carbon atom has eight electrons in its outer shell and all electrons are paired.

Formula (III) is equivalent to the more conventional formula in which the two carbon atoms are doubly bonded, $\text{H}_2\text{C} = \text{CH}_2$. Such formulas with double bonds were used many decades before any electronic conception of valence bonds existed. They satisfactorily explain the fact that unsaturated hydrocarbons always have an even number of hydrogen atoms per



Model of Ethylene Molecule

molecule, and predict the correct number of isomers of higher members of the series. Formulas for propylene and three butylenes are indicated below.



Theory predicts five structurally isomeric amylenes C_5H_{10} , 13 structural isomers C_6H_{12} , and 27 structural isomers C_7H_{14} . These compounds are known in exactly the right numbers and the structure of each has been established by methods which we will be in a position to understand shortly.

Free Radicals. While it is true as indicated above that such substances as CH_3 do not exist as compounds capable of isolation and analysis, an important development of recent years involves the experimental proof that molecular fragments of this type actually exist momentarily and can be produced by heating the vapors of various organic compounds, or by other means. Paneth has used metallic mirrors to detect the presence of these highly active molecules. Under suitable conditions gases containing the free radicals when passed over such mirrors (heated) remove the metallic films and deposit metal-alkyls

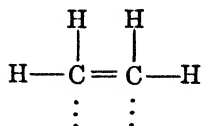
farther on in a cooler portion of the tube. The reactivity of free methyl, ethyl and methylene radicals is indicated by the fact that their half periods (time necessary for half of the amount present to disappear) under experimental conditions are in the order of a few thousandths of a second. These free radicals play an important part in many organic reactions particularly those taking place at elevated temperatures.

Significance of Double Bonds. The ordinary representation of the double bond should not be interpreted too literally. Suppose we consider a long chain hydrocarbon with a double bond somewhere near the middle of the chain. Interpreting the picture mechanically, one might conclude that the position of the double bond would be the strong part of the chain and that the chain would break more readily at any position other than at the double bond. Actually, the situation with respect to many reactions is quite different from this because there are a number of reagents which can be used to cleave the chain (ozone is one) and it is *at the double bond*, rather than elsewhere that cleavage takes place. However, double bonds appear in general to be more resistant to thermal decomposition than single bonds.

Considering the formula from the electronic point of view, we note that two pairs of electrons are involved in the double linkage, and it would be reasonable to suppose that they might interfere with each other and thus cause reactivity. We do know that there is a "crowded condition" in the molecule at a double bond and that the two carbon atoms are drawn closer together in ethylene (1.34Å, interatomic distance) than in ethane (1.54Å). We also know that more energy resides in a double bond than in a single bond and that this energy is released when the bond is broken.

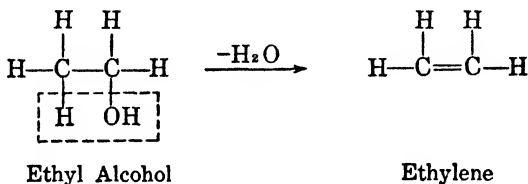
In order to account for the reactivity of the double bond Thiele¹ many years ago expressed the idea that in double bonds not all of the valence was used up in holding the two carbon atoms together but that a part of the valence was free and caused reactivity. He pictured the structure of ethylene as follows:

¹ Johannes Thiele (1865-1918) was professor of Chemistry at the University of Strassburg.



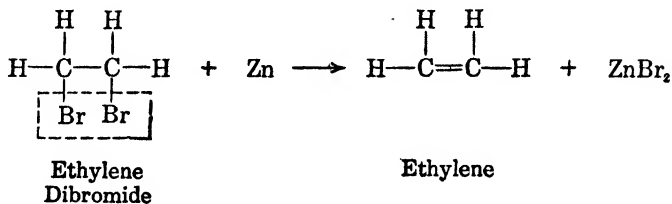
in which the dotted lines represent the free "partial valences."

Preparation of Ethylene Hydrocarbons. Ethylene as well as the higher alkenes may be prepared in a variety of ways. The most useful method for the laboratory preparation is by dehydration of the appropriate alcohol (p. 79).



The reaction can be effected by passing the alcohol over alumina or similar material at 350-400°. Alcohols may be dehydrated at lower temperatures using chemical dehydrating agents such as concentrated sulfuric acid, potassium hydrogen sulfate (KHSO_4) or phosphorus pentoxide.

The introduction of a double bond may be accomplished by treating an alkyl halide with certain basic reagents as indicated in the discussion on the structure of ethylene. Compounds containing two halogen atoms situated on adjacent positions in the carbon chain may be dehalogenated using a bivalent metal, usually zinc.

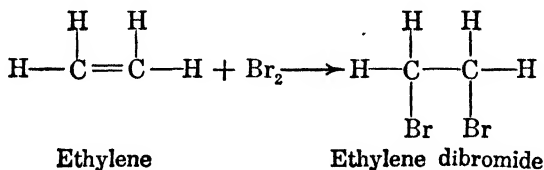


Alkenes are obtained commercially as by-products of the cracking of petroleum to produce gasoline (p. 26). They are

also produced by the catalytic dehydrogenation of the corresponding alkanes.

Reactions of Ethylene Hydrocarbons. The simplest of the ethylene hydrocarbons is very much like the others in chemical properties and shows the characteristic property of the series, namely, unsaturation. This unsaturation or ability to take up other atoms is due to the reactive double bond discussed in a previous section. The alkenes are able to add on directly without loss the following important reagents: (1) hydrogen in the presence of a catalyst, (2) halogens, least readily iodine, (3) halogen acids, most readily hydriodic acid, (4) sulfuric acid, (5) hypochlorous acid, HOCl , and (6) ozone, O_3 . In the case of some unsaturated compounds, hydrocyanic acid, or even water, may be added. In addition there are other less common reagents which may add. Oxidation is brought about rather easily, in which the effect may be that of the addition of two hydroxyl groups or the formation of an oxide.

The addition of halogens takes place much more rapidly than the substitution of halogens in the hydrocarbons of the methane series. The addition of bromine produces one of the two possible dibromoethanes, known as ethylene dibromide, and the reaction may be pictured as follows:

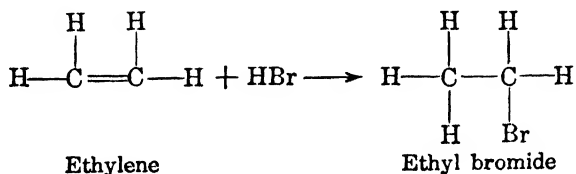


One might expect bromine to act on the ethylene by substitution, because there are hydrogen atoms attached to carbon just as in the methane series, which might be substituted. Such a reaction does take place readily at high temperatures even to the exclusion of the addition reaction but at low temperatures the addition reaction takes place more rapidly and all the bromine reacts by addition before the substitution reaction has proceeded to

any extent (p. 55). If equal volumes of gaseous bromine and ethylene are mixed under ordinary conditions, the reaction goes practically as shown above. If, however, more than an equal volume of bromine is used, the excess, in the presence of light, will replace hydrogen atoms, one at a time, and if sufficient bromine is present, the compound C_2Br_6 will eventually be formed.

The addition of a halogen to unsaturated compounds is so characteristic that the reaction is used as a test for unsaturation.

The addition of halogen acids produces compounds which are identical with the monosubstitution products of ethane. Ethylene and hydrogen bromide produce ethyl bromide.

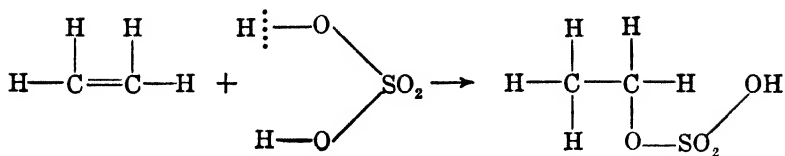


When higher alkenes add hydrogen bromide (or other halogen acids) they may do so to produce two different products. Propylene, for example, adds HBr to yield isopropyl bromide along with a small amount of *n*-propyl bromide. This is in accord with Markownikoff's rule² that the positive group adds on the carbon atom which is linked to the largest number of hydrogen atoms. It is obvious that there is a directing influence (polarity) present in the original molecules.

In 1933 it was found that oxygen and peroxides have a profound effect on the addition of HBr to unsaturated compounds (Kharasch). These catalysts may practically completely reverse the direction of addition and yield a result in direct contradiction to Markownikoff's rule. This phenomenon has not been noted for the other halogen acids.

Concentrated sulfuric acid adds in a manner similar to the halogen acids in which one of the hydrogen atoms of the acid becomes attached to the carbon atom with the most hydrogens and the rest of the molecule attaches to the other.

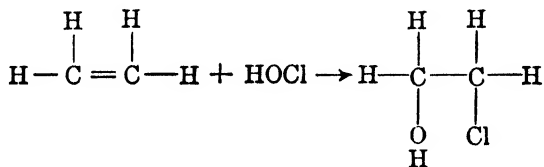
² Vladimir Markownikoff (1838-1904) was professor of Chemistry at the University of Kazan.



Ethyl sulfuric acid

Diethyl sulfate may be formed by the reaction of ethyl sulfuric acid with ethylene. Alkyl sulfates are important intermediates in the production of alcohols (p. 69).

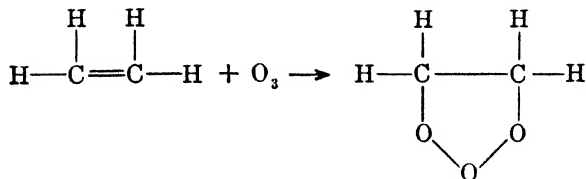
Hypochlorous acid with ethylene forms a substance known as a chlorohydrin, according to the equation.



Ethylene chlorohydrin

The reaction between propylene and hypochlorous acid yields about 90 per cent $\text{CH}_3\text{CHOHCH}_2\text{Cl}$ and 10 per cent $\text{CH}_3\text{CHClCH}_2\text{OH}$. This distribution of products would be expected from Markownikoff's rule.

With ozone ethylene yields an *ozonide* which may be formulated as follows:

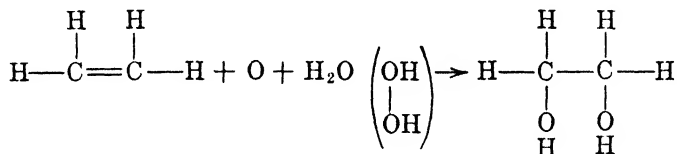


The ozonides of unsaturated hydrocarbons when treated with water (with zinc dust added to reduce the peroxide formed) react in such a way as to break the carbon chain and yield two molecules of oxygen derivatives (aldehydes or ketones) which are to be studied later. These derivatives can be identified, the lengths of their chains determined, and the position of the double bond in the original hydrocarbon thus located.

The mechanisms of addition reactions of the alkenes are by no means definitely established, nor is it certain that the same type of mechanism is involved in the different reactions. The reaction of bromine and ethylene is predominantly a surface reaction and does not take place readily in the gaseous phase. This indicates that the reaction in this case is not simply the result of molecular collision. The reaction is generally thought to be a step-wise process with the positive bromine (Br^+Br^-) reacting with the more negative carbon to which the double bond is attached followed by addition of the negative ion to the other carbon.

In the addition of acids to ethylene the *ions* may actually add. It is true that acids in the ionized condition (in water solution) are not added readily, but this may be due to the hydration of the ions (particularly the hydrogen ion) which prevents their addition. For a discussion of this and related questions see for example Remick "Electronic Interpretations of Organic Chemistry."

The unsaturated hydrocarbons are very readily oxidized as compared with paraffins. Aqueous permanganate, for example, will oxidize alkenes at ordinary temperature. If carefully carried out the reaction may proceed as follows, using ethylene as an example.



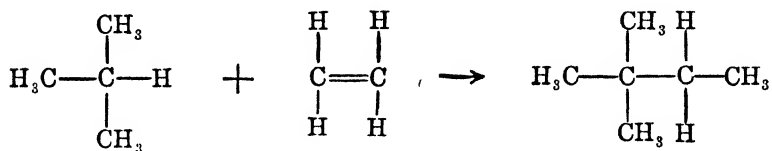
The evidence for the structure of the product will be given later. If oxidation is continued under somewhat more vigorous conditions the carbon chain of an alkene will break and acids which can be identified are formed. This constitutes a second (often less satisfactory) method for locating the position of a double bond in a higher alkene. When ethylene and oxygen (or air) are passed over a silver catalyst at high temperatures the ethyl-

ene is oxidized to ethylene oxide, $\begin{array}{c} \text{O} \\ \diagup \quad \diagdown \\ \text{CH}_2-\text{CH}_2 \end{array}$ (p. 234).

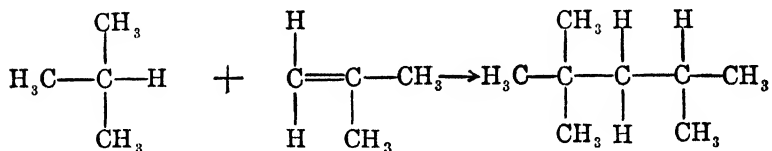
Most of the preceding reactions take place at relatively low temperatures. When alkenes are brought to high temperature

they will react with numerous other reagents. Among the more important addition reactions are those involving the alkylation of paraffins and aromatic hydrocarbons (benzene, p. 406).

Ethylene and isobutane react in the presence of acid catalysts to yield 2,2-dimethylbutane:

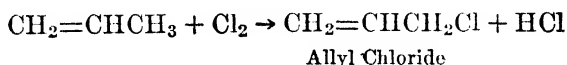


Isobutane and isobutylene yield "isoöctane."



Both of the above products are of value as anti-knock gasoline constituents.

At temperatures above about 300° propylene reacts with halogens by substitution instead of by addition.



Under similar conditions ethylene yields vinyl chloride ($\text{CH}_2=\text{CHCl}$).

Uses of Ethylene. Ethylene is a tremendously important chemical since it is the starting material for more than fifty chemicals of industrial importance. Some of these chemicals, which include alcohol and ether, are also made by competitive methods. A number of the important chemicals derived from ethylene will be discussed in Chapter XV.

Ethylene has two direct uses which are of interest. Its usefulness as an anesthetic has been demonstrated in recent years and it has been widely used. It may also be used in bringing about the ripening of all varieties of fruits, blanching of celery,

etc. An important application is made on a large scale in the citrus fruit industry where exposure to a low concentration of ethylene is a common practice. It is interesting that a real ripening of fruits is induced, that is, the sugar content of the fruits rises and the objectionable substances (such as tannins in unripe persimmons) disappear. Tomatoes one inch in diameter ripen in about a week's exposure, more mature fruits ripen much faster. Higher unsaturated hydrocarbons have effects similar to those of ethylene.

Propylene, the butenes and the pentenes are used extensively for the production of alcohols (p. 83). They are also used for the alkylation of benzene (p. 425) and the production of high octane gasoline. The uses of these compounds will be expanded greatly in the next few years because of the recent advances in the technology of their production and separation.

Nomenclature. The simpler alkenes are often called by names similar to those given the paraffin hydrocarbons, except that the ending *ane* is changed to *ylene*. Thus we have propylene, butylene, etc. The systematic method of naming modifies the name for the paraffins, by substituting the ending *ene*; ethene, propene, butene, etc. The members with branched chains are named in a manner similar to that used for the saturated hydrocarbons in that the substance is named as a derivative of the unsaturated hydrocarbon corresponding to the longest continuous chain of carbon atoms. The position of the double bond in a chain is designated by a number which corresponds to the first doubly bonded carbon counting from the end of the chain. The carbon atoms in the continuous chain are numbered so that the number indicating the position of the double bond is as small as possible. The more common and the systematic names of the alkenes are given in the table on page 58.

The alkenes are frequently referred to as *olefins* or *olefinic* hydrocarbons. The term "olefin" (oil forming) is derived from the fact that when treated with chlorine or bromine the lower members yield oily liquids.

Alkadiene Series (Diolefins, Dienes)

In the unsaturated hydrocarbons so far mentioned, only one double bond is present per molecule. Hydrocarbons with two and three double bonds are called alkadienes (dienes) and alkatrienes (trienes) respectively. Examples are given in the accompanying table. In all the instances cited the double bonds are *conjugated* (p. 289).

As would be expected these compounds in general add on the same reagents as the alkenes, and the number of moles added is the same as the number of double bonds present.

Butadiene ($\text{CH}_2=\text{CHCH}=\text{CH}_2$) is of particular interest because it can be polymerized to yield elastoprenes (synthetic rubber). This polymerization consists of the molecules adding to each other successively, usually along with some other co-present unsaturated compound, to yield very long elastic molecules (p. 396). Butadiene was produced in hundreds of thousands of tons during World War II from petroleum by the dehydrogenation of butane and from ethyl alcohol by a catalytic process.

Isoprene ($\text{CH}_2=\text{C}(\text{CH}_3)\text{CH}=\text{CH}_2$) is also of great interest because natural rubber as well as a large number of other important natural compounds are built up from isoprene units. A number of these will be mentioned later. Isoprene itself can be polymerized to yield rubber but it has not been developed extensively on a commercial scale partly because of difficulties in producing it economically.

Methyl isoprene ($\text{CH}_2=\text{C}(\text{CH}_3)\text{C}(\text{CH}_3)=\text{CH}_2$) was used during World War I for producing methyl rubber, which was inferior to natural rubber. This diene is made by dehydration of pinacol (p. 117) which in turn is produced by reduction of acetone.

In each of the three alkadienes there is present what are termed *conjugated* double bonds. When double bonds alternate with single bonds in this way peculiar behavior appears. This will be discussed later (p. 289). Heating dienes which do not possess conjugated double bonds causes them to migrate (if

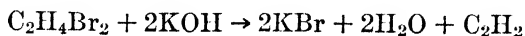
possible) to yield conjugated systems. Compounds are more stable when the double bonds have this relationship.

UNSATURATED HYDROCARBONS

	Melting Point °	Boiling Point °	Density 20/4
<i>Alkenes</i>			
Ethylene (Ethene) $\text{CH}_2=\text{CH}_2$	-169.4	-103.9	.5699 (-103.9)
Propylene (Propene) $\text{CH}_3\text{CH}=\text{CH}_2$	-185.2	- 47.6	.5148
α -Butylene (1-Butene) $\text{CH}_3\text{CH}_2\text{CH}=\text{CH}_2$	- 6.3	.5952
β -Butylene (2-Butene) <i>cis</i> $\text{CH}_3\text{CH}=\text{CHCH}_3$..	-139.3	3.6	.6213
β -Butylene (2-Butene) <i>trans</i> $\text{CH}_3\text{CH}=\text{CHCH}_3$	-105.8	0.9	.6042
Isobutylene (2-Methylpropene) $(\text{CH}_3)_2\text{C}=\text{CH}_2$	-140.7	- 6.9	.5942
Amylene (1-Pentene) $\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}=\text{CH}_2$..	-138.0	30.1	.6410
1-Hexene $\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}=\text{CH}_2$	-141.0	63.7	.6734
1-Heptene $\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}=\text{CH}_2$	-120.0	92.8	.6968
<i>Alkadienes</i>			
Propadiene (Allene) $\text{CH}_2=\text{C}=\text{CH}_2$	-136.1	- 34.3	.6575 (-30)
1,3-Butadiene $\text{CH}_2=\text{CHCH}=\text{CH}_2$	-108.9	- 4.5	.6206
2-Methyl-1,3-butadiene (Isoprene) $\text{CH}_2=\text{C}(\text{CH}_3)\text{CH}=\text{CH}_2$	-146.8	34.1	.6805
<i>Alkatienes</i>			
1,3,5-Hexatriene $\text{CH}_2=\text{CHCH}=\text{CHCH}=\text{CH}_2$	- 11.0	81.	.7754
2,6-Dimethyl-4-methene-2,5 heptadiene	55.
$ \begin{array}{ccccccc} & & \text{H} & & \text{H} & & \\ & & & & & & \\ \text{H}_3\text{C}-\text{C}=\text{C}-\text{C}=\text{C}-\text{CH}_3 \\ \quad \quad \quad \quad \\ \text{CH}_3 \quad \text{CH}_3 \quad \text{CH}_3 \end{array} $			

Acetylene Series (Alkynes)

If the substance $\text{CH}_2\text{BrCH}_2\text{Br}$, obtained from the action of bromine on ethylene, is heated with alcoholic potassium hydroxide solution, the reaction represented by the following equation takes place.

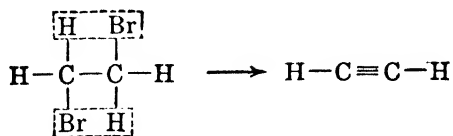


Ethylene
dibromide

Acety-
lene

This reaction is similar to one cited as a method for the preparation of ethylene. The substance C_2H_2 is a gas, the molecular

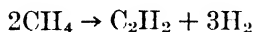
formula of which is determined by the general method already outlined. The reaction could be most simply pictured as the abstraction of the equivalent of two molecules of hydrogen bromide from the original molecule as indicated below:



A triple bond means three electron pairs between the two carbon atoms. In order for these six electrons to be held jointly by two carbon atoms they are drawn together closer (1.20\AA) than in alkenes. To form a triple bond requires a large amount of energy, which is released when the bond is broken. In keeping with the above formula acetylene and its homologs add two and finally four atoms. Higher members of the series and other derivatives may be satisfactorily formulated in accordance with the structure theory and on the basis of the triple bond.

Acetylene (Ethyne) owes its extreme importance in organic chemistry to the fact that it can be made cheaply and used as a starting material for producing many highly important compounds including acetaldehyde and acetic acid (p. 100). Its most important direct use is in oxy-acetylene welding. No other member of the homologous series even remotely approaches it in importance.

Its most important source is by treating calcium carbide (calcium acetylide), CaC_2 , with water. The carbide is itself made by heating lime and coke together in an electric furnace. Potential or actual competing methods for making acetylene involve (1) passage of hydrocarbons through an electric arc and (2) catalytic decomposition of methane (natural gas) according to the equation

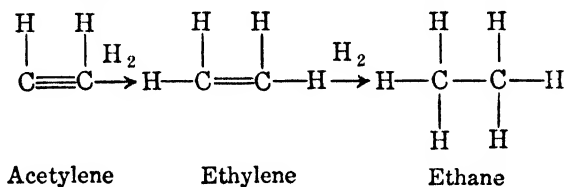


Acetylene can be liquefied but cannot safely be handled in this condition as it may explode violently to yield carbon and hydrogen. It is shipped and handled in acetone solution in containers containing porous material.

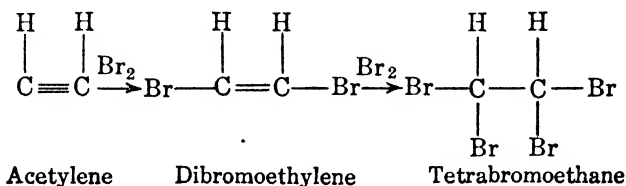
Acetylene-air mixtures explode violently. Explosive mixtures may contain as little as 3 per cent or as much as 82 per cent acetylene. In contrast methane forms explosive mixtures with air only in the range 5-13 per cent methane.

The homologous series of hydrocarbons all exhibit similar properties, and in general show the same addition reactions as shown by the "ethylenes." They never take up less than two atoms or groups, and if they take up only two the resulting compound is still unsaturated and can enter into further addition reactions with additional reagent. Curiously, acetylenes do not enter into addition reactions quite as readily as do the alkenes. They are systematically named similarly to the paraffin hydrocarbons except that the names end in *yne*, as ethyne, propyne, etc.

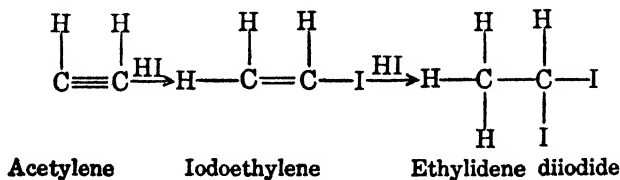
Acetylene can be reduced by the action of hydrogen in the presence of a catalyst, producing first ethylene and finally ethane.



When brought in contact with bromine, acetylene forms first a dibromoethylene and finally symmetrical tetrabromoethane.



The addition of halogen acids takes place *unsymmetrically* in the manner indicated.

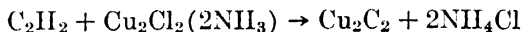


Whenever two molecules containing unlike radicals are added successively the resulting product is likely to have an unsymmetrical structure.

The most important addition reaction of acetylene, the addition of water, will be discussed later (p. 100).

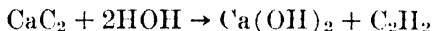
The acetylene hydrocarbons are easily oxidized, but the products formed on incomplete oxidation are numerous and variable.

Acidic Properties of Acetylene. Acetylene and its homologs show very weak acid properties and form insoluble salts with certain metals. The reaction with cuprous chloride is used as a test for the acetylene hydrocarbons.



This reaction takes place immediately if acetylene comes in contact with an ammoniacal solution of cuprous chloride, and a characteristic red precipitate is formed. Silver acetylide, Ag_2C_2 , is precipitated under similar conditions in the presence of a silver salt. These reactions appear to involve ionic interchange. Cal-

cium acetylide (carbide) $\begin{array}{c} \text{Ca} \\ \diagup \quad \diagdown \\ \text{C} \equiv \text{C} \end{array}$ has the non-volatile property of a salt and is a conductor of electricity in the fused state, like other salts. It may be considered then to be the calcium salt of the very weakly acidic acetylene. On this basis its reaction with water (hydrolysis) would be expected to go practically to completion because the acetylene formed is both volatile and very little ionized. The reaction actually goes rapidly to completion.



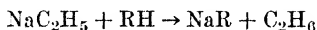
Sodium and other salts of acetylene behave in a similar fashion.

The slight ionization of acetylene may be attributed to the crowding together of the two carbon kernels which exert a relatively large pull on the electrons and allow the separation of protons. It should be noted that the ion which remains when either one or two protons are lost from acetylene has completed octets:



Hydrogen acetylide ion (—) Acetylide ion (—)

Various other unsaturated and saturated hydrocarbons demonstrate some acidic properties particularly in their ability to form metallic derivatives (for example with sodium) and to undergo interchange reactions with other metallic derivatives. A salt of an extremely weakly acidic hydrocarbon, such as NaC_2H_5 , will react with numerous hydrocarbons, practically all of which have stronger acidic properties than ethane, as follows:

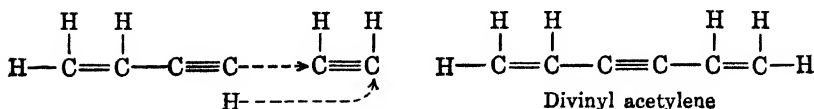


It should be noted that such a reaction follows the laws of ionic interchange in that the *least ionized* compound (hydrocarbon) is formed.

Acetylene hydrocarbons in which no hydrogen is attached to a triply bonded carbon atom do not show the characteristic ionization of acetylene. It is interesting that when a higher hydrocarbon with a triple bond in the center of the chain is heated in solution with sodium amide NaNH_2 to about 200° it is changed slowly into the corresponding acetylene with the triple bond at the end and an ionizable hydrogen. Under these conditions hydrogen atoms become detached from the carbon atoms and may migrate (presumably stepwise) along the chain past several carbon atoms.

Polymerization of Acetylene. When passed through a red hot tube acetylene molecules undergo polymerization whereby the ring compound benzene, C_6H_6 , is formed.

Acetylene undergoes another type of polymerization when absorbed in a solution of cuprous and ammonium chlorides, which is more interesting and important than the benzene polymerization. The products formed include vinyl (vīnil) acetylene and divinyl acetylene. These are formed by the direct addition of two and three molecules of acetylene respectively.

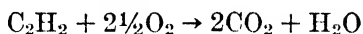


Both these hydrocarbons polymerize (pōl'ī-mēr-īz) readily, particularly the latter, to form compounds of unknown high molecular weight. Other less highly unsaturated hydrocarbons often polymerize but not so readily as the compounds under discussion. Vinyl acetylene is used in a process for making a valuable type of synthetic rubber (p. 395).

Thermochemistry of the Hydrocarbons. If a gram atom of carbon (12 grams) and four gram atoms of hydrogen (4 grams) are burned, a total of 229.9 large calories of heat are produced. Of this total 94.3 calories is from the burning of the carbon and 135.6 calories from hydrogen. If the equivalent quantity of methane gas (16 grams) is burned, 210.9 calories are produced. This shows that the heat of combustion of the uncombined elements is greater than the heat of combustion of the elements when combined in methane. If then carbon and hydrogen were made to combine to form methane, heat would be given out: $229.9 - 210.9 = 19$ calories per gram molecule.

If the heat of combustion of two gram atoms of carbon (188.6 calories) and two gram atoms of hydrogen (67.8 calories), which together amount to 256.4 calories, be compared to the heat of combustion of an equivalent amount of acetylene, 312 calories, it will be seen that the combined elements in acetylene have more energy than the uncombined elements. Therefore, to change the uncombined elements into the compound, heat would have to be added. The heat of formation of acetylene from the elements is therefore -55.6 calories per gram molecule. In burning a gram molecule of acetylene, 55.6 calories more heat are given out than would be given out by the burning of an equivalent amount of carbon and hydrogen. This additional energy is stored up in the triple bond, a strained condition which is the seat of potential energy, and which on burning is changed into heat energy.

Flame Temperatures. Acetylene when mixed with oxygen burns according to the equation

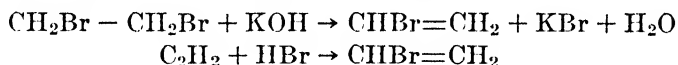


Thus it produces three volumes of gas from each volume of gas burned. When ethane burns, however, 5 volumes of gas are produced for each volume of ethane burned. The temperature

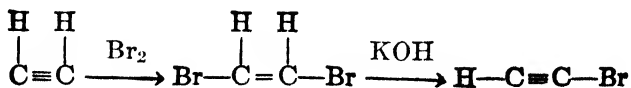
of a flame depends both on the amount of heat that is generated, and upon the heat that must be used up to heat the reaction products, so that although ethane per unit volume produces more heat than acetylene (373 Cal per mole as compared with 312 for acetylene), the products of combustion are in larger quantity, and they take up that heat and cool what would otherwise be a hotter flame. Acetylene yields the hottest flame of any ordinary fuel. The relatively high temperature which is possible in a hydrogen-oxygen flame is not due to a high molecular heat of combustion (only 58 calories per gram molecule when the water is not condensed), but more particularly to the fact that the amount of the products of combustion is a minimum. The hottest flame known derives its energy from the combination of hydrogen atoms (Langmuir) and produces only one mole of product (H_2) for every two moles of reactant—*i.e.*, atomic hydrogen.

Unsaturated Halides

Halogen substitution products of the unsaturated hydrocarbons have not in general been made by the action of halogens on the hydrocarbons themselves. Recently, however, conditions have been found under which it is possible to accomplish such results technically (p. 55). They may be made by other methods, for instance, according to the equations:



The substance formed in these reactions is called vinyl bromide and is an intermediate product in the first method cited for making acetylene. $\text{CBr}=\text{CH}$ is also known and has been prepared as indicated below.



In connection with the reactivity of organic halides it is interesting to note that one of the type of vinyl bromide, $\text{CH}_2=\text{CHBr}$, in which the halogen is attached directly to the doubly bonded

ACETYLENE HYDROCARBONS

	Boiling Point °
Acetylene (ethyne, ethine) $\text{HC}\equiv\text{CH}$	1 (at 48 atmos.)
Methyl acetylene (propyne) $\text{CH}_3\text{C}\equiv\text{CH}$	-23.5
Dimethyl acetylene (2-butyne) $(\text{CH}_3)_2\text{C}\equiv\text{CCH}_3$	27
Ethyl acetylene (1-butyne) $\text{C}_2\text{H}_5\text{C}\equiv\text{CH}$	18
Methyl ethyl acetylene (2-pentyne) $\text{CH}_3\text{C}\equiv\text{CC}_2\text{H}_5$	55
<i>n</i> -Propyl acetylene (1-pentyne) $\text{CH}_3\text{CH}_2\text{CH}_2\text{C}\equiv\text{CH}$	48
Isopropyl acetylene (3-methyl-1-butyne) $(\text{CH}_3)_2\text{CHC}\equiv\text{CH}$	28
Methyl <i>n</i> -propyl acetylene (2-hexyne) $\text{CH}_3\text{CH}_2\text{CH}_2\text{C}\equiv\text{CCH}_3$	84

DI-ACETYLENES

Dipropargyl (1,5-hexadiene) $\text{HC}\equiv\text{CCH}_2\text{CH}_2\text{C}\equiv\text{CH}$	85
Dimethyl di-acetylene (2,4-hexadiene) $\text{CH}_3\text{C}\equiv\text{C}-\text{C}\equiv\text{CCH}_3$	130

HYDROCARBONS WITH DOUBLE AND TRIPLE BONDS

Vinyl acetylene $\text{H}_2\text{C}=\text{CHC}\equiv\text{CH}$	6
Divinyl acetylene $\text{H}_2\text{C}=\text{CHC}\equiv\text{CCH}=\text{CH}_2$	

HALOGEN DERIVATIVES OF THE UNSATURATED HYDROCARBONS

Vinyl chloride (chloroethene) $\text{CH}_2=\text{CHCl}$	-18
Vinyl bromide (bromoethene) $\text{CH}_2=\text{CHBr}$	16
Acetylene dichloride (1,2-dichloroethene) $\text{CHCl}=\text{CHCl}$	55
Acetylidene dichloride (unsymmetrical) $\text{CH}_2=\text{CCl}_2$	37
1,1-dichloroethene)	
Tetrachloroethylene (tetrachloroethene) $\text{OCl}_2=\text{CCl}_2$	121
Tetraiodoethylene (tetraiodoethene) $\text{CI}_2=\text{CI}_2$	—
Monochloroacetylene (chloroethyne) $\text{HC}\equiv\text{CCl}$	Explosive
Allyl chloride $\text{CH}_2=\text{CHCH}_2\text{Cl}$	45.7
Chloroprene (2-chloro-1,3-butadiene) $\text{CH}_2=\text{CCl}-\text{CH}=\text{CH}_2$	47

carbon atom, is characteristically unreactive especially in replacement reactions. The interatomic distance between carbon and bromine is less than is the case with alkyl bromides. On the other hand, halides of the type such as allyl bromide, $\text{CH}_2=\text{CH}-\text{CH}_2\text{Br}$, in which the halogen is one carbon atom removed from the doubly bonded carbon, are *more* reactive than the corresponding saturated halides.

PROBLEMS

1. There are two isomeric substances with the molecular formula $\text{C}_2\text{H}_4\text{Br}_2$. What are their full structural formulas? Indicate how each can be prepared from unsaturated hydrocarbons.

2. What is the type formula for the acetylene hydrocarbons? For the dialkenes?

3. Metallic zinc reacts with ethylene dibromide (1,2-dibromoethane). What products would you expect to be formed?

4. What weight of bromine would be taken up by (a) 1 gram of C_2H_4 (b) 1 gram of $\text{C}_2\text{H}_2\text{Br}_2$?

5. A hydrocarbon gas combines directly with its volume of chlorine gas. The addition product shows a molecular weight of 112.92. What is the molecular formula of the original gas?

6. How might zinc be used in the preparation of acetylene?

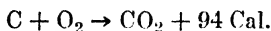
7. When hydroxyl groups are attached to non-metallic elements, the compounds are generally acids. On this basis would you expect the addition product of ethylene and sulfuric acid to be an acid? A mono- or di-acid?

8. Suppose 70 cc. of HBr gas at standard conditions is added to 30 cc. of C_2H_4 . What will be the volume after the reaction takes place provided that all of the addition product condenses to the liquid state. If acetylene was used in the place of ethylene, what would be the final volume on the same assumption?

9. How could you distinguish by a simple test between vinyl acetylene and divinyl acetylene?

10. Why is it that burning of pentane with a heat of combustion of 841 calories per gram molecule produces a flame of about the same temperature as burning of methane, which has a heat of combustion of 211 calories per gram molecule?

11. If the following thermochemical equations hold, how much heat is evolved when a gram molecule of carbon monoxide is burned?



12. Picture a space model of an acetylene molecule.

13. A compound C_8H_8 is formed by the polymerization of vinyl acetylene. Write a probable formula.

14. Is the process mentioned in problem 17 exothermic or endothermic? (Heat of combustion of ethylene = 331.6 Cal.). Is the equilibrium shifted in favor of the formation of ethylene by high or low temperature?

15. What products would be finally formed if 10 cc. of C_2H_4 gas were mixed with 80 cc. of Cl_2 and allowed to stand in diffused sunlight? How much 0.1 N NaOH solution would be required to neutralize the mixture?

16. When 2,2,4-trimethylpentane (p. 19) is made commercially from isobutylene (in cracking gas), an octene is formed as an intermediate product. Indicate the probable course of the reactions.

17. Methane from natural gas can be used (pyrolysis) as a source of ethylene and hydrogen. Give a possible interpretation of this result in terms of free radicals.

CHAPTER V

ALCOHOLS

The alcohols show more diverse types of reactions than any compounds so far studied. They are used as solvents and can be the starting materials for the production of almost any organic chemical. In some textbooks on organic chemistry they are discussed first and made the "center" of organic chemistry for this reason. Alcohols were more important as starting materials in earlier decades than now, because whereas they formerly were obtained entirely from other sources, now many alcohols are derived from the *hydrocarbons*.

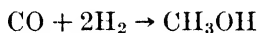
Before the advent of petroleum cracking and synthetic methanol, the only alcohols available in quantity were methyl alcohol (methanol) from wood distillation and the two fermentation products ethyl alcohol and fusel oil. The fusel oil is a mixture of amyl (C_5) alcohols and small amounts of lower members and its supply was limited. Now the list of available alcohols is much larger, most of them are available in unlimited quantities and none of them *need to be made* by the original processes.

Methanol, Methyl Alcohol, wood alcohol, CH_3OH . This compound may be regarded as the first oxidation product of methane, in which one of the carbon valences is now attached to oxygen. Methanol is so much more easily oxidized than methane that it is impossible to stop the reaction effectively at that point. By using a large concentration of methane in comparison to the oxygen (analogous to the procedure mentioned in connection with chlorination p. 32) it is possible to obtain a conversion of as high as 30 per cent of the methane oxidized into methanol. This is a minor commercial source of methanol.

Methanol can be made as already indicated by the alkaline treatment of a methyl halide (p. 36). While this throws light on its structure it is not a useful way of preparing methanol. Methyl halides are usually made from methanol, not *vice versa*.

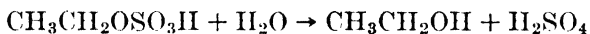
Wood contains compounds containing many *methoxyl* groups ($\text{CH}_3\text{O}-$) which break off on heating in the absence of air to form methanol. This was the older source of methyl alcohol (wood alcohol), but at present only about 10 per cent of commercial methanol comes from wood.

A revolutionary development so far as methanol and other alcohols is concerned was the process for synthesis of methanol from carbon monoxide and hydrogen.



The reaction is made to take place at about 400° and 200 atmospheres pressure in the presence of oxide catalysts. Such catalysts have been developed largely on an experimental basis. One which is effective is a mixture of the oxides of copper, zinc and chromium. Various by-products of the reaction including other alcohols are formed and the amounts can be modified by changing conditions and catalysts. A number of the by-products could become principal products if it were desired. The other alcohols which are formed include ethanol, propanol, isopropyl alcohol, isobutyl alcohol, and 2,4-dimethyl-pentanol-3.

Ethyl alcohol, Ethanol, or grain alcohol, $\text{C}_2\text{H}_5\text{OH}$, is the next member of a homologous series of alcohols. It may be made, in the presence of an alkali, by the action of water on monohalogen substitution products of ethane, but here again the necessary halogen compounds are not ordinarily obtainable except as they are made from ethyl alcohol itself. The alcohol is made industrially by the hydration of ethylene and by alcoholic fermentation. The hydration of ethylene by direct addition of water has not as yet been developed sufficiently to be a practical method. The hydration is achieved, however, by the hydrolysis of ethyl sulfuric acid or diethyl sulfate, formed by absorption of ethylene in 98-100 per cent sulfuric acid (p. 52).



The alcohol is formed upon dilution of the absorption liquor with about an equal amount of water. The alcohol is removed by

distillation along with appreciable amounts of diethyl ether (p. 88) which is formed as a by-product unless especial precautions are taken.

The principal industrial source of alcohol is the fermentation with yeast of diluted molasses, malted grain extracts, and other sugar-containing solutions. By this means it can be produced cheaply and it is very often the starting material for the production of more complex organic chemicals. The fermentation reaction is complex and will be discussed later; grain alcohol is one of the many substances formed, and is purified by fractional distillation in complicated and efficient stills. The resulting product is, however, a mixture of about 96 per cent alcohol and 4 per cent water, due to the fact that such a mixture boils at a constant temperature lower than the boiling point of pure alcohol. In order to obtain pure alcohol the constant boiling mixture, containing about 96 per cent alcohol, may be treated with an excess of quick lime, CaO , which reacts with the water present to form calcium hydroxide, from which the pure alcohol can be distilled. It is only by prolonged treatment that alcohol of high purity is obtained. Such "absolute" alcohol is very hygroscopic and if exposed to the air will take up water. Alcohol is generally considered "absolute alcohol" if it contains less than one per cent water.

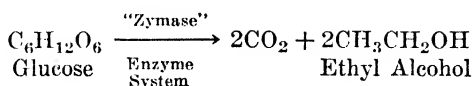
Absolute alcohol is readily prepared industrially from ordinary alcohol by mixing it with benzene and distilling. A ternary mixture boiling at 64.85° comes over first, containing alcohol 18.5 per cent, benzene 74.1 per cent, and water 7.4 per cent. This is followed by a binary mixture of benzene and alcohol leaving pure alcohol as a residue. Ethylene dichloride and similar compounds are also used for this purpose in place of benzene.

Pure alcohol has a specific gravity of .793 at 15° . It might be supposed that it would be possible to calculate the specific gravity of a water solution containing any percentage of alcohol. This would be true were it not for the fact that when alcohol and water are mixed a contraction in volume occurs and the mixture has a higher specific gravity than the calculated value. The specific gravities of alcohol-water mixtures have, however, been

determined experimentally and the percentage of alcohol in a sample of unknown alcohol content can be determined by comparing its specific gravity with the specific gravities which have been determined for known samples. This method cannot be relied on when other substances than water and alcohol are present. When sugars are present in a sample of unknown alcohol content, it is necessary to distill it to get a sample free from sugars. The temperature has a great effect upon the specific gravity of alcohol samples so that it is necessary to control the temperature carefully when specific gravities are being measured.

Denatured alcohol is ordinary alcohol to which has been added poisonous or ill-tasting substances in order to render it unfit for consumption. There are two types of denatured alcohol, *completely denatured alcohol* which is sold tax free to the public without restrictions, and *specially denatured alcohol* which can be obtained tax free only by firms under bond engaged in certain lines of manufacturing. An important formula for completely denatured alcohol consists of alcohol 100 parts, wood alcohol 2 parts, pyridine bases $\frac{1}{4}$ part, kerosene (benzine) $\frac{1}{2}$ part. One of the most important specially denatured alcohol formulas is, ethyl alcohol 100 parts, wood alcohol 5 parts.

Manufacture of Alcohol. The yearly production of industrial alcohol in U. S. amounts to about 600,000,000 gallons. The most important raw product for its production is "blackstrap" cane molasses, the residue from cane sugar refining. One volume of the molasses is diluted with about five gallons of water, and to each 1000 gallons of this "wort" is added about 1 gallon of sulfuric acid. By these simple operations the material is ready to be seeded with yeast. In case corn or other grain is the raw material out of which the alcohol is made, it must be ground, cooked, and treated with malt, by which enzyme action converts the starch into soluble sugars, etc., before it is ready for the fermenter.

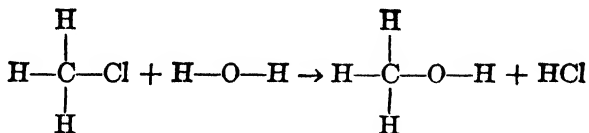


The diluted molasses is placed in a tank, preferably of iron, with a capacity which may be as high as 200,000 gallons, and a suitable quantity of pure yeast of a suitable strain is added. The yield of alcohol is much affected by the strain of yeast. Foreign organisms produce undesirable by-products, so this factor must be carefully controlled. The

acidity of wort is favorable for yeast but is unfavorable for most bacteria. The fermenter may be covered and fitted with an exit pipe through which the evolved carbon dioxide is led to pumps for compression. One ton of molasses on fermentation yields about 520 lbs. of carbon dioxide (Dry Ice) which is a valuable by-product. The temperature of the fermenter at the start may be 78° F. in which case the heat caused by the fermentation will at the end bring the temperature up to about 100° F. A better method is to introduce cooling coils into the fermenter and carry out the entire fermentation at about 90° F. The "beer" which results after about three days' fermentation contains 7 to 9 per cent alcohol. The distillation of this dilute alcohol for the production of the various grades of marketable alcohol is too complicated to be described here and the student is referred elsewhere.¹ Fusel oil consisting of higher boiling alcohols is an important by-product. The first stages of the distillation are usually carried out as continuous processes, but the final rectification for the production of the higher grades of alcohol is frequently carried out in a discontinuous still. The alcohol is denatured for industrial purposes as indicated above.

The yeast which grows during the fermentation of the diluted molasses, under the conditions described, is of little or no commercial value. When compressed yeast for bread-making is the principal product desired the wort is much more dilute, a different strain and a larger amount of yeast is used for seeding, and the wort is aerated during fermentation. Under these conditions one gallon of molasses may produce 4-4½ lbs. of yeast and 0.6 gallon of 50 per cent alcohol. The beer after fermentation, however, contains only about 1 per cent alcohol and is usually not distilled for the production of concentrated alcohol, but is used for vinegar manufacture.

Structure of the Alcohols. We obtain some idea of the arrangements of atoms in methanol molecules from the fact that methanol can be obtained by the reaction between methyl chloride and water.

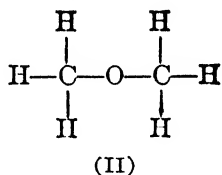
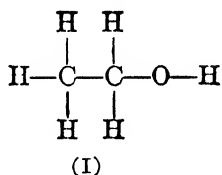


The arrangement given is the simplest one and we have definite evidence that it is the correct one. In the *formula*, one of the four hydrogen atoms has a different situation from the others.

¹ Young, "Distillation Principles and Processes," The Macmillan Co.

Correspondingly in the *compound* only one fourth of the hydrogen present can be replaced by metallic sodium. The formula shows the presence of the hydroxyl group and the compound acts like other compounds in which hydrogen must be attached to oxygen. Methanol, like all other hydroxyl compounds, reacts with phosphorus pentachloride to give a compound in which the chlorine takes the place of the hydroxyl group. The product, methyl chloride, CH_3Cl , is identical to that which may be obtained by the action of chlorine on methane. This fact as well as others, including the method of preparation, indicates that the formula given above fits the substance called methyl alcohol or methanol.

The structure of ordinary alcohol can be worked out in the same manner. In this case there are two possible simple arrangements corresponding to the formula $\text{C}_2\text{H}_6\text{O}$.

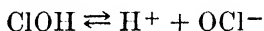


In the first case one of the hydrogen atoms is differently situated than the other five, in the second case all six hydrogen atoms are situated alike. In grain alcohol one sixth of the hydrogen is replaceable by metals, so the first formula corresponds to the substance while the second does not. In all other respects also this formula seems to fit, and pictures grain alcohol as similar in structure to methanol. There is a corresponding similarity between other reactions of the two alcohols. (There is another substance $\text{C}_2\text{H}_6\text{O}$ whose properties are in accord with formula (II), in that none of the hydrogen in the compound is replaceable by metals, but all of the hydrogen alike may be replaced by treatment with chlorine gas. It will be studied later.)

Formulation of higher alcohols in accordance with the formulas given for methyl and ethyl alcohols is entirely successful. On the basis of the formulas one would predict the existence of two propyl alcohols, four butyl alcohols, eight amyl alcohols, and

seventeen hexyl alcohols. Exactly the right number exists in each case and the structures of all have been established.

Significance of the Hydroxyl Group. It is possible that the student will have associated the presence of hydroxyl groups with bases exclusively. If so, this conception will have to be discarded as structural formulas are adopted, for we find that hydroxides of non-metals usually are acids and not bases. The way in which a substance ionizes determines whether it is an acid or base, not the grouping of atoms in the undissociated molecules. Thus NaOH ionizes as a base while ClOH ionizes as an acid.

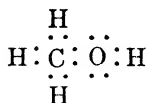


The manner in which the substance ionizes depends on the element or group to which the hydroxyl group is attached. ClOH, hypochlorous acid, is usually written HClO in inorganic chemistry to emphasize its acid property and HOCl in organic chemistry to emphasize its behavior in addition reactions (p. 53).

The majority of acids contain oxygen and these oxygen acids so far as we know all contain hydroxyl groups, that is they have hydrogen attached to oxygen. The hydrogen which is attached to oxygen is in general the ionizable hydrogen. Taking familiar members of each group of the periodic table as examples, the hydroxides of sodium and calcium are bases only, the hydroxide of aluminum is basic and also acidic (amphoteric), while the hydroxides of carbon, nitrogen, sulfur, and chlorine are acidic. Carbon tetrahydroxide or orthocarbonic acid $\text{C}(\text{OH})_4$ is unstable and breaks down to form water and the familiar (but unstable) carbonic acid $\text{CO}(\text{OH})_2$. Acids derived from nitrogen, sulfur and chlorine which correspond to carbonic acid are $\text{NO}_2(\text{OH})$, nitric acid; $\text{SO}_2(\text{OH})_2$, sulfuric acid, and ClO_3OH , perchloric acid. From this it can be seen that the presence of the hydroxyl group in the structural formula does not signify anything as to the basic or acidic character of the compound. We shall find the hydroxyl group in the structural formulas of both organic acids and bases. The ability to produce hydrogen

ions (hydronium ions, H_3O^+) and hydroxyl ions respectively in water solution characterize acids and bases.

Ionization of Alcohols. The breaking down of a molecule into ions is favored when there is a union in the molecule between a metallic and a non-metallic atom which can separate forming ions with completed electron shells. From this standpoint let us consider the case of methanol as being typical of the alcohols.



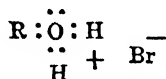
The point of greatest contrast in the molecule is between the hydrogen and oxygen and by the separation of a proton (hydrogen ion) the oxygen shell remains complete. We might expect ionization at this point. The point of next greatest contrast is between hydrogen and carbon, for while carbon is not strongly non-metallic, hydrogen is distinctly so. Here again if protons were to separate, the shell of the carbon atom would remain complete. From our previous discussion of methane which has a similar structure and which does not have acidic properties sufficient to react with metallic sodium we may expect ionization between carbon and hydrogen to be non-existent or at most infinitesimal.

The point of least contrast is between the elements carbon and oxygen both of which are non-metallic but differ in degree. Here if a separation took place forming a hydroxyl ion, the carbon atom would be left with only a sextet of electrons—a highly unstable structure.

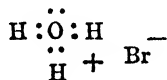
Experimentally there is abundant evidence to indicate the *alcohols ionize feebly as acids and do not give rise to hydroxyl ions.*

According to Brønsted's conception and definition (which is highly valuable in many cases) an acid may be defined as anything which gives off protons (hydrogen ions) and a base anything which accepts protons. Hydroxyl ions, NH_2^- ions, OCH_3^- ions are according to this definition strong bases; NH_3 and acetate ions are weaker and Cl is an extremely weak base.

In the sense of this definition only, an alcohol is a base, because there is evidence that the oxygen of the hydroxyl group can accept a proton to form an "oxonium salt" which may be formulated as follows:

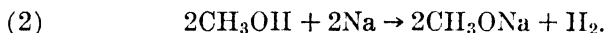
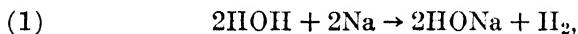


Such salts are unstable, and compare in structure with the "oxonium salts" formed between water and acids:



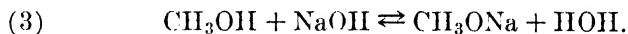
The structure at the left is the hydrated hydrogen ion (H_3O^+) which is thought to exist in water solutions of acids. Above at the left is represented an *alcoholated* hydrogen ion.

Chemical Properties—Similarity to Water. The alcohols are in several respects like water. Just as inorganic salts often have water of crystallization, so they may have "alcohol of crystallization." An example of this is $\text{CaCl}_2 \cdot 4\text{C}_2\text{H}_5\text{OH}$. Alcohols are like water in that they react with metallic sodium, potassium, calcium, etc., with the liberation of hydrogen gas, as shown by the equations—



The reaction with alcohols is less violent than the reaction with water.

The same product, NaOCH_3 , is formed to a small extent when methyl alcohol and sodium hydroxide are put together.



This reaction does not take place to any appreciable extent if there is a quantity of water present, for it is highly reversible. Sodium methoxide, NaOCH_3 , is in other words almost completely hydrolyzed into sodium hydroxide and methyl alcohol in the presence of water. Reaction 3, above, is in reality a neutralization reaction forming a salt and water and so far as we know

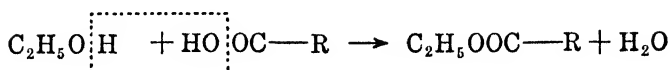
takes place instantaneously. The sodium methoxide is a solid substance, a good conductor of electricity and highly ionized when in alcohol solution and has all the general characteristics of salts. It is, however, the salt of an extremely weak acid, and shows this by the fact that the salt is almost completely hydrolyzed by a small amount of water.

The degree of ionization of methanol as an acid is about $\frac{1}{4}$ that of water. It is therefore not able to affect indicators. Introduction of an alcohol into water which is more highly ionized, does not increase the hydrogen ion concentration. Water may be called an acid (as well as a base) since it furnishes hydrogen ions in very low concentrations. It is only in this same sense that alcohols may be regarded as acidic. We do not ordinarily speak of water and alcohol as "acids" though water does ionize very slightly to give H^+ and OH^- ions, and alcohol ionizes in lesser amount into H^+ and OC_2H_5^- ions.

Reaction with Acids. Certainly one of the most important reactions of the alcohols is with acids to produce *esters*. These compounds will be considered more extensively in a later chapter but it is desirable here to discuss briefly the general character of the reactions and the products. Superficially the reaction between an alcohol and an acid resembles that between a base and an acid (neutralization), but the resemblance is only superficial.

There are several outstanding ways in which esterification differs from neutralization: (1) the alcohols, as we have indicated, do not ionize as bases; (2) esterification is slow whereas neutralization is always rapid even when the acids or bases involved are weak; (3) the products (esters) unlike salts are volatile and do not give evidence of any ionization (salts in general ionize freely); (4) application to esterification of the laws which hold for neutralization, leads to confusion and direct contradictions.

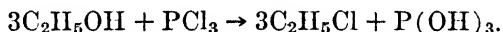
Perhaps the most convincing proof that esterification is fundamentally different from neutralization is the experimentally demonstrated fact that in certain esterifications involving oxygen containing acids the *hydrogen* is furnished by the *alcohol* and the *hydroxyl* by the *acid*.



There are a number of evidences supporting this statement, the most conclusive of which involves the use of isotopic oxygen with atomic weight 18, and tracing its fate in the reaction. The questions naturally arise: what kind of a reaction is esterification if it is not neutralization and what kind of a substance is an ester if it is not a salt? The answers are simply these: Esterification involves the interaction of two acidic *molecules* (acid and alcohol) and the product of the reaction is a mixed acidic anhydride (p. 162). This idea will be further amplified and its value pointed out in a later chapter. It should be made clear here, however, that anhydride formation (from acids) is slow like esterification and esters are like acid anhydrides in that they are volatile, non-ionized and react with water to yield acids. Furthermore the generalizations which apply to anhydride formation and decomposition also apply to esterifications.

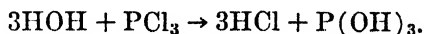
Further consideration of these problems will be postponed until after organic acids have been studied. Until they have been studied we can only say that alcohols react with acids in general and there are many esters derived from each alcohol.

Reaction with Phosphorus Halides. Phosphorus trichloride, PCl_3 , and phosphorus pentachloride, PCl_5 , react with alcohols to replace the hydroxyl group with a chlorine atom. Other reactions take place at the same time, but the first reaction mentioned above is pictured by the equation:



Other phosphorus halides react with alcohols in a similar manner. Phosphorus pentachloride is a more active agent than phosphorus trichloride and will react with some substances containing the hydroxyl group, which are not affected by phosphorus trichloride.

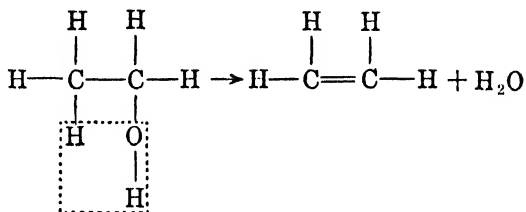
Phosphorus trichloride reacts with water in a manner analogous to its reaction with alcohols:



By this reaction hydrochloric and phosphorous acids are formed as indicated, and the hydroxyl group of the water is replaced by chlorine. Phosphorus trichloride may then be regarded as a mixed anhydride of phosphorous and hydrochloric acids.

When acid anhydrides are studied in more detail later, it will be noted that alcohols generally react with the more reactive anhydrides just as water does. Thus we see a further resemblance between the alcohols and water.

Dehydrating Agents. When ethyl alcohol for instance is heated with a strongly dehydrating agent like phosphorus pentoxide or concentrated sulfuric acid, the formation of ethylene,

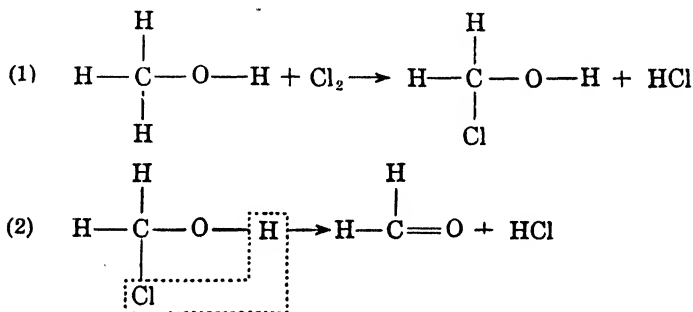


C_2H_4 , takes place. The dehydrating agent takes the elements of water out of the alcohol. This is the most convenient laboratory method for preparing ethylene gas, and is a very general reaction of alcohols. *In general when a hydroxyl group and a hydrogen atom are on adjoining carbon atoms, they may be removed by strong dehydration regardless of the make-up of the rest of the molecule.* In more complicated compounds the removal of water may take place merely by heating without the presence of a dehydrating agent.

Oxidation. Alcohols are fairly susceptible to oxidation and may be oxidized by agents which will not affect the saturated hydrocarbons. Practically any of the agents listed below are sufficiently strong to bring about oxidation of an alcohol. Complete oxidation can be effected under proper conditions, with the production of carbon dioxide and water. If, however, the oxidation is carried on at lower temperature and in solution, aldehydes, ketones, and acids are formed as intermediate products. These compounds will be the subjects of study in later chapters.

In the oxidation of an alcohol the carbon atom which holds the oxygen (hydroxyl group) is the one on which more oxygen attaches itself. The initial step in the oxidation may be regarded as an entering wedge which facilitates further oxidation.

The effect of halogens on alcohols is partially illustrated by their effect on methyl alcohol. Methyl alcohol would be expected to react with either chlorine or bromine in the manner indicated in equation (1).



The product formed is, however, unstable. A chlorine atom and a hydroxyl group will not remain on the same carbon atom, but hydrogen chloride breaks off as indicated (2), leaving oxygen alone attached to the carbon atom. The net result is the same as is obtained when the alcohol is oxidized with some other reagent which gives up oxygen directly.

Oxidation is often thought of as involving a removal of electrons from the element in question. Thus in the oxidation of copper the element loses two electrons whether it is attacked by oxygen, chlorine or some other non-metallic element. The oxidation of sulfur dioxide to sulfur trioxide, for example, is somewhat different as no ions are formed and sulfur presumably possesses the same number of electrons after oxidation as it did previous to oxidation. Nevertheless electrons may, in one sense, be removed, that is they may be shifted from a position close to the sulfur kernel to a position nearer the oxygen kernel. Such a shift presumably takes place whenever an element becomes attached to a more non-metallic element. Only in certain cases is there a complete removal of electrons. In most organic oxidations electrons are thought to be shifted away from carbon atoms because the carbon atoms become attached to more strongly non-metallic elements. The carbon atoms thus increase their positive valence. Numerically the valence of

carbon both in methane and carbon dioxide is four but during the oxidation the valences are changed one by one from negative to positive through the shifting of the four pairs of valence electrons. Thus when methane is oxidized to methanol *two* electrons may be regarded as shifted from the carbon atom and the total change in valence of the carbon atom is therefore two. In methane we may say carbon has a valence of four negative; in methanol three negative and one positive, or a net negative valence of two. In dichloromethane, a carbon's net valence may be said to be zero since two valences are positive and two are negative.

The **oxidizing agents** which are most commonly used in organic chemistry are mentioned below. They oxidize organic compounds forming various organic oxidation products, depending on the substance oxidized, the character of the medium in which the oxidation is carried on, the temperature, and the amount of the oxidizing agent used, etc. Many other oxidizing agents may also be used for particular oxidations.

In **dichromates** (*e.g.*, $K_2Cr_2O_7$) or **chromic anhydride** (CrO_3) chromium changes its valence from six positive to three positive when heated (in acid solution) with an oxidizable organic compound.

In **nitric acid** nitrogen may reduce its positive valence from five to either three or two, and salts of nitric acid behave similarly.

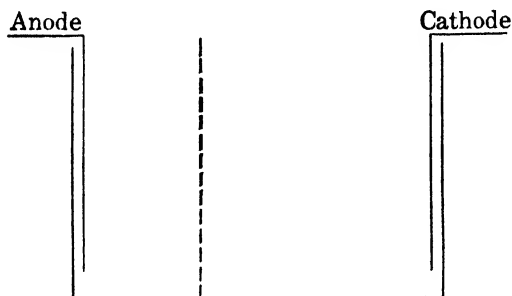
Manganese in a **permanganate** may change its valence from seven positive to four positive (in alkaline solution) or to two positive (in acid medium). Halogens either free or in the presence of water may act as oxidizing agents. Each halogen atom may be said to change its valence from zero to one negative. **Peroxides** (*e.g.*, H_2O_2) are sometimes used as oxidizing agents. Oxygen in this case may be said to change its valence from one negative to two negative.

When it is desired to bring about **complete oxidation** as in an analysis, **copper oxide** is most often used and may lose one half or all its oxygen. **Sulfuric acid** at high temperatures is also an effective oxidizing agent for the complete destruction of many organic compounds. In the oxidation sulfuric acid is converted into sulfur dioxide.

Electrolytic Oxidation or Reduction. Oxidation of organic compounds may be accomplished by electrolytic methods. It will be recalled that when a solution of sulfuric acid, for instance, is electrolyzed, hydrogen is liberated at the negative electrode and oxygen at the positive electrode. The oxygen and hydrogen may be said to be liberated in the "nascent" condition and if oxidizable substances are in the region of the anode where oxygen is liberated, they are oxidized. Likewise reduction may take place in the cathode region.

When electrolysis is taking place in any solution electrons are being removed at the anode and introduced at the cathode. Hence in the anode region oxidations take place while the reverse process (reduction) takes place near the cathode.

The following figure shows diagrammatically how a cell for carrying out an oxidation may be constructed. The whole cell may be filled with a sulfuric acid solution and to the anode compartment is also added the substance to be oxidized. In the electrolysis the SO_4^{--} ions travel to the anode, are discharged, and may then be pictured as decomposing into sulfur trioxide and atomic oxygen. The atomic oxygen because of its affinity for electrons oxidizes the organic compound and the sulfur trioxide combines with water to regenerate sulfuric acid. The diaphragm of some porous material is introduced to prevent the oxidizable substance from diffusing into the region of the cathode where it might be reduced. In case one desires to reduce a compound electrolytically it is placed in the cathode chamber.



In order to carry out a particular oxidation (or reduction), suitable materials and conditions must be used. The composition of electrodes, diaphragms, the potential differences and current densities used, as well as the choice of the electrolyte, etc., cannot be discussed here.²

Higher Alcohols. Although the general properties of the alcohols can well be studied by paying attention to only one or two simpler alcohols, the higher alcohols have structural features which make their behaviors distinctive. There is a gradation of physical properties as in other homologous series and a general tendency toward unreactivity on the part of higher alcohols. This is particularly noticeable in the reactions with metallic sodium and the existence of decreasing acidic properties has been confirmed by electromotive force measurements. A few of the

² See Creighton and Fink, "Principles and Applications of Electro Chemistry," 2 vols., John Wiley and Sons.

more important individual higher alcohols are discussed briefly below. In addition to the specific methods of preparation indicated, all of these alcohols and many more can be prepared by use of the Grignard reagents (Chapter IX) and by hydrogenation of aldehydes and ketones (Chapter VII).

Isopropyl alcohol, petrohol, is made by hydration of propylene (petroleum cracking). It is an excellent solvent and since it has very little odor and similar properties, it is used extensively as a substitute for ethyl alcohol. Isopropyl alcohol is used extensively in the less expensive anti-freezes and a 70 per cent solution in water is used as "rubbing" alcohol. It is also catalytically dehydrogenated to yield acetone (p. 115).

n-Butanol is produced by anaerobic fermentation of corn, a process developed during World War I for the production of acetone. Though produced in larger quantity than the acetone, it was then a by-product. Now butanol esters are so important in the lacquer and plastics industries that the acetone is considered the by-product.

Sec. Butyl alcohol is made by the hydration of *n*-butylene and is catalytically dehydrogenated to yield methyl ethyl ketone.

Tert. Butyl alcohol may be produced in quantity by the hydration of isobutylene, but has not as yet found important uses.

Amyl alcohols, pentanols (Pentanol) are prepared industrially by the hydrolysis of the mixture of chlorides resulting from the high temperature vapor phase chlorination of the pentane fraction of natural gasoline (p. 32). The chlorides are hydrolyzed at 150-170° using 30 per cent sodium hydroxide and 1-2 per cent sodium oleate. The sodium oleate serves as a "catalyst" by reacting more readily with the primary chlorides than does the sodium hydroxide. The resulting ester (p. 165) is then hydrolyzed by the hydroxide very rapidly to regenerate the sodium oleate and produce the desired alcohol. The net result is a greatly increased rate of primary alcohol formation. The oleate also provides more intimate contact by emulsifying the two immiscible layers present (amyl chloride layer and water layer). *n-Amyl alcohol* (pentanol) may be separated

from the mixture of alcohols and utilized separately. These alcohols either separately or as mixtures are used as solvents and plasticizers (p. 381) and for the production of amyl acetate, an important lacquer solvent.

Isoamyl alcohol, *3-methyl-1-butanol* is the chief amyl alcohol present in fusel oil and is obtained from this source.

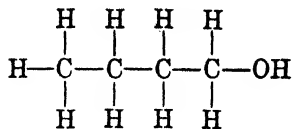
2-Pentanol (80 per cent) and *3-pentanol* (20 per cent) compose a mixture of alcohols known as "*sec*-amyl alcohol" which is obtained by the sulfuric acid method from the normal pentenes present in the pentane-pentene fraction of cracked gasoline.

Lauryl alcohol, *1-Dodecanol*, $C_{12}H_{25}OH$, is made by the hydrogenolysis at high temperature and pressure of lauric acid esters from cocoanut oil (p. 167) and is used in making important new detergents (p. 145).

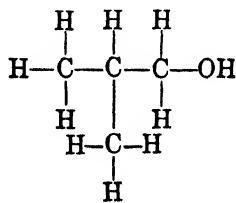
Cetyl (sé'til) *alcohol*, $C_{16}H_{33}OH$, the sixteenth member of the normal series occurs both free and combined in several natural waxes. Its palmitic acid ester is the chief constituent of spermaceti.

Ceryl alcohol, $C_{26}H_{53}OH$, and *myricyl alcohol*, $C_{30}H_{61}OH$, are two natural occurring sterols. The most important sterols, however, especially from the biological standpoint, have more complex ring structures and will be mentioned later.

Primary, Secondary, and Tertiary Alcohols. The four butyl alcohols have the following formulas and illustrate three different types.

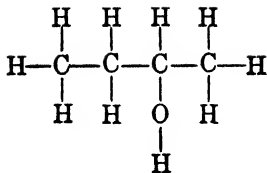


(Normal)

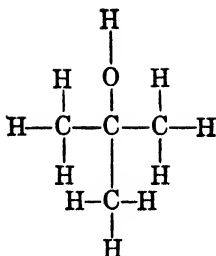


(Iso)

Primary

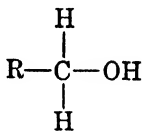


Secondary

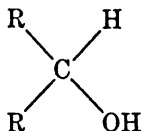


Tertiary

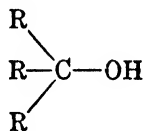
From these formulas will be seen the difference between primary, secondary, and tertiary alcohols. Primary alcohols all contain the group $-\text{CH}_2\text{OH}$, secondary alcohols all contain the bivalent group $>\text{CHOH}$, while tertiary alcohols have the trivalent group $\equiv\text{COH}$.



Primary



Secondary

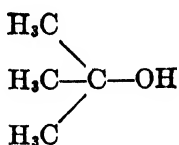


Tertiary

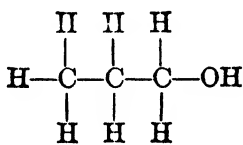
The "R" in the above formulas represents any alkyl group and in the first case may represent hydrogen as well. Isopropyl alcohol is the simplest secondary alcohol and tertiary butyl alcohol is the simplest tertiary alcohol. In reacting with halogen acids (in which reactions the hydroxyl groups are lost from the alcohol) the tertiary alcohols act most rapidly, the secondary next and the primary the slowest. In dehydration, in which the hydroxyl is also lost, tertiary alcohols react very readily as compared with secondary or primary alcohols. With organic acids such as acetic acid, the primary alcohols react most rapidly (hydrogen rather than hydroxyl is lost in this case, p. 77), the secondary next and the tertiary the slowest. In acidic properties the primary alcohols are much the strongest, the secondary next and the tertiary weakest.

The oxidation of primary, secondary and tertiary alcohols yield different types of products as will be discussed in Chapter VII.

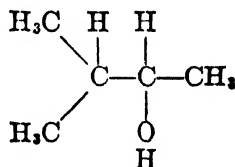
Nomenclature. Simpler alcohols are named from the group which is attached to the hydroxyl, like methyl, ethyl, and propyl alcohols. Systematically they are named from the corresponding hydrocarbons by use of the ending *ol*, as for instance methanol, ethanol, 1-propanol, 2-propanol, 1-butanol, etc. The carbon atoms in the continuous chain are numbered so that the number indicating the position of the hydroxyl group is as small as possible. Alcohols have historically also been named as the substitution products of methyl alcohol, which in this connection, especially, may be called *carbinol*. Thus we have *trimethyl carbinol*, *ethyl carbinol*, and *methyl iso-propyl carbinol*, respectively represented by the formulas given below. It is important to note that in all systems of naming, the suffix *ol* is used to designate compounds containing the hydroxyl group.



Trimethyl carbinol
(2-methyl-2-propanol)



Ethyl carbinol
(propanol)



Methyl iso-propyl carbinol
(3-methyl-2-butanol)

ALCOHOLS

	Formula	Density	Boiling Point	Solubility in 100 ml.		
				Water	Alc.	Ether
Methyl alcohol ..	CH_3OH	.796 (20°)	64.5	Inf.	Inf.	Inf.
Ethyl alcohol ...	$\text{C}_2\text{H}_5\text{OH}$.789 (20°)	78.4	"	"	"
Propyl alcohol, <i>n</i> ..	$\text{CH}_3\text{CH}_2\text{CH}_2\text{OH}$.804 (20°)	97.4	"	"	"
Propyl alcohol, <i>iso</i> ..	$\text{CH}_3\text{CH}(\text{OH})\text{CH}_3$.789 (20°)	82.8	"	"	"
Butyl alcohol, <i>n</i> ..	$\text{CH}_3(\text{CH}_2)_3\text{CH}_2\text{OH}$.810 (20°)	117.	8.3	"	"
Butyl alcohol, <i>sec</i> ..	$\text{CH}_3\text{CH}_2\text{CHOHCH}_3$.819 (22°)	99.8	12.5 (20°)	"	"
Butyl alcohol, <i>tert</i> ..	$(\text{CH}_3)_3\text{COH}$.781 (25°)	82.9	Inf.	s.	"
Butyl alcohol, <i>iso</i> ..	$(\text{CH}_3)_2\text{CHCH}_2\text{OH}$.806 (15°)	108.4	9.5 (18°)	Inf.	"
Amyl alcohols	$\text{C}_5\text{H}_{11}\text{OH}$.814-.824	102.5-137	2.7-16.7	"	"

PROBLEMS

1. Construct the formulas for all the alcohols having the formula $C_5H_{11}OH$. Name each as a derivative of methyl alcohol (carbinol). How many belong to each class, primary, secondary, and tertiary? Name the same alcohols as substitution products of hydrocarbons.

2. What weight of water is formed by the complete burning of one ml. of alcohol?

3. What are the signs of the valences of carbon in (1) methyl chloride, (2) methanol, (3) carbon tetrachloride, (4) carbonic acid.

4. Write the structural formulas of (1) the hydriodic acid ester of ethyl alcohol, (2) the nitric acid ester of methanol.

5. Picture how an ester of phosphoric acid could be formed as a by-product of the action of phosphorus pentachloride on ethyl alcohol.

6. How many ces. of chlorine measured at standard conditions would be necessary to carry the oxidation of one gram of methyl alcohol through one step?

7. If 4.5 grams of metallic sodium is allowed to react with absolute ethyl alcohol, how many grams of HCl gas in solution would be necessary to neutralize the $NaOH$ formed by the hydrolysis of the $NaOC_2H_5$?

8. One gram of a simple alcohol when treated with metallic sodium liberated 244 cc. of hydrogen gas at standard conditions. What is the molecular weight of the alcohol?

9. How much ethylene gas at 24° and 740 mm. could theoretically be obtained from 1 liter of 96 per cent alcohol?

10. How much "cleaning solution" containing 2.5 g. of CrO_3 per liter would be rendered ineffective by 0.5 gram of methyl alcohol?

11. Why does commercial absolute alcohol sometimes have an odor of benzene? Can this be removed by distillation? How?

12. By "change of valence method" or other method which you use in inorganic chemistry, balance an equation in which ethylene is oxidized by dilute permanganate in the absence of acid.

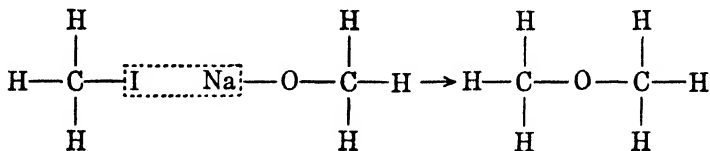
13. Alkyl radicals are heavier and occupy more space than hydrogen atoms. Considering the molecular type of reaction involved in esterification, what reason is there for the difficulty of esterification of tertiary alcohols?

14. Is the synthesis of methanol exothermic or endothermic? How is the equilibrium affected by temperature and pressure? Why is a catalyst necessary? (Heat of combustion of methanol, 170.9 Cal.)

CHAPTER VI

ETHERS

If methyl iodide, CH_3I , and sodium methoxide, NaOCH_3 , are warmed together, a reaction takes place, with the formation of sodium iodide and an organic substance which would be expected to have the formula indicated.



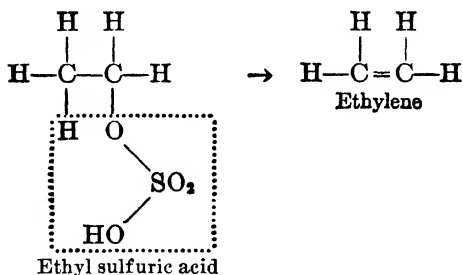
The gaseous substance which is formed in this way is called *dimethyl ether*, and shows itself to be an isomer of ordinary alcohol, in that it gives the same results on elemental analysis and has the same molecular weight. All evidence points to the correctness of the structure given above. The methoxide ion OCH_3^- is probably the reacting substance, just as the OH^- ion was in the case previously cited (p. 36).

Dimethyl ether is the simplest member of a homologous series of *ethers*, and has recently been used as a refrigerant in "quick freezing." The member of the series that is of greatest importance is diethyl ether, or ordinary *ether*, which has the formula $\text{C}_2\text{H}_5-\text{O}-\text{C}_2\text{H}_5$ and is a derivative of ordinary alcohol. It may be made by the interaction of ethyl iodide and sodium ethoxide,¹ similar to the dimethyl ether mentioned above, but it can be made much more economically directly from alcohol.

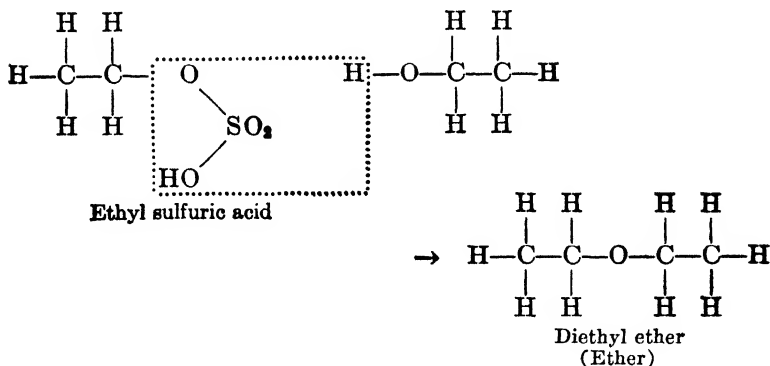
It will be recalled that ethylene is made by the action of sulfuric acid on alcohol, and by varying the conditions, ether may be made from the identical reagents. *In either case*, the alcohol and sulfuric acid react first to form water and an ester of sulfuric

¹ This method of preparing ethers was discovered by A. W. Williamson (1824-1904) in 1852, and is sometimes known as Williamson's synthesis. Williamson was an English chemist, professor in the University College in London.

acid; *i.e.*, a mixed anhydride of alcohol and sulfuric acid. When this mixture is heated to about 140° , some of the water passes off and the ethyl sulfuric acid decomposes as indicated into ethylene and sulfuric acid. Since sulfuric acid is regenerated, the net result is the elimination of the elements of a molecule of water



from the alcohol molecule. If, on the other hand, the ethyl sulfuric acid is heated to about 130° in the presence of extra quantity of alcohol, the two react thus:

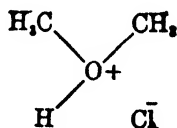


Sulfuric acid is again regenerated with the net result that the elements of a molecule of water are abstracted from two molecules of alcohol.

In addition to the two methods already mentioned ether may also be produced from alcohol by passing the vapor over alumina catalyst at 200° - 300° or by partial hydration of ethylene under similar conditions. Ether is also obtained as a by-product in the production of ethyl alcohol from ethylene.

Ether is an anhydride of alcohol, and has the behavior characteristic of the anhydrides of very weakly acidic substances. It is very stable and unreactive. Ethers can be hydrolyzed to produce alcohols, but this happens only under extreme conditions in the presence of an acid which acts as a catalytic agent. Ethers can also be oxidized and yield products similar to those formed from alcohols, but these reactions are not important. Ethyl ether (ordinary ether) is a volatile liquid, boiling a little below body temperature. It is used very extensively for an anesthetic, and in the chemical laboratory is used almost entirely as a solvent. The use of ethers as chemical reagents is unimportant.

With hydrogen chloride, dimethyl ether forms an interesting addition compound which throws some light on the valency of oxygen. The compound may be formulated as follows:



and may be called dimethyl oxonium chloride. It bears the same relationship to dimethyl ether as ammonium chloride does to ammonia. We shall discuss more critically in a later chapter the structure of compounds of this type.

Solvent Properties. The wide application of ether as a solvent depends on several factors: (1) it is readily available in large quantities at a low cost, being made directly from alcohol, (2) it is unreactive and hence does not react with the substances which it dissolves, (3) many types of organic substances dissolve in ether, and (4) it is a low boiling substance which can be easily removed from less volatile material. The fact that ether is only slightly soluble in water and forms a separate layer makes it possible to "extract" substances, which are readily soluble in ether, from water in which they are slightly soluble. The ether solution can then be separated from the water solution by means of a separatory funnel.

We have relatively little knowledge of why certain substances are soluble in one solvent and not in another, or why some sub-

stances are so nearly insoluble in all solvents. One of the most important generalizations is the fact that as a rule *like substances are mutually soluble*. This refers to physical solution in which no marked chemical change takes place, and does not apply to the obviously chemical reactions involved when a metal is "dissolved" in an acid, or when an acid which is practically insoluble in water is "dissolved" in a sodium hydroxide solution. Organic compounds which are similar in composition and in structure are soluble in each other. Hydrocarbons dissolve other hydrocarbons, alcohols dissolve other alcohols, esters dissolve other esters, etc. It must not be inferred, however, that a substance is soluble only in its own particular type of compound, for this is by no means true.

Organic substances which possess the hydroxyl (OH) grouping of atoms are soluble in water or alcohol which also possess this same grouping. Thus C_2H_5OH is soluble in water in all proportions, while CH_3OCH_3 , its isomer, is relatively insoluble. Higher alcohols are not soluble in water, as the hydroxyl group is so small a part of the molecule that the molecule as a whole is not like water. Substances which contain oxygen (or nitrogen) in addition to carbon and hydrogen are more soluble in ether, for instance, than they are in a hydrocarbon, containing as it does only carbon and hydrogen. This is an advantage of ether over a hydrocarbon mixture such as "petroleum ether," which is sometimes used as a solvent. The petroleum ether is even more inert than the ether, but because its molecules contain only carbon and hydrogen, it will not freely dissolve compounds containing oxygen and nitrogen.

Water is an important solvent, even for organic substances, especially those of lower molecular weight and those containing a large proportion of hydroxyl groups. For fats and oils and many other materials, ether or some other organic compound is necessary as a solvent. Most of the simpler organic substances are soluble either in water or in ether. Substances like alcohol which resemble both ether and water in composition or structure are soluble in all proportions in both.

Another general rule which is useful is that substances with high molecular weight are usually less soluble in the ordinary,

low molecular weight, solvents than are the compounds with low molecular weight. The simplest compounds with very low molecular weights are more often soluble in all the ordinary solvents including water.

Distribution Between Immiscible Solvents. When a third substance is agitated with a mixture of equal amounts of immiscible solvents it distributes itself between the two solvents in such a way that the ratio of its concentrations in the two phases is a fixed value, and equal to the ratio of its solubility in one solvent to its solubility in the other. In practical work this useful relationship holds only approximately, especially where the solute is present in large concentrations. In this case its presence may modify the character of one or both of the solvents materially. Actually solvents are never *completely* immiscible, and partial miscibility makes the situation more complex.

The use of this principle in laboratory practice may be illustrated by a case in which a substance is to be extracted from a water solution by chloroform in which it is ten times as soluble as it is in water. One extraction with an equal volume of chloroform will remove 10/11 of the substance from the water phase. If only $\frac{1}{4}$ volume of chloroform is used the ratio of concentrations is the same, *i.e.*, 10 to 1, but the ratio of the total quantities is 2.5 to 1, and the fraction of the total solute in the chloroform phase is $2.5/3.5$ or 72.4 per cent. Two extractions with the same amount of chloroform brings the total removal up to 91.8 per cent.

Isopropyl ether, $((\text{CH}_3)_2\text{CH})_2\text{O}$, is a by-product in the manufacture of isopropyl alcohol from propylene and has become available as a commercial solvent. Its higher boiling point, 67.5° , makes it more easily handled without losses from evaporation, and the larger hydrocarbon radical makes it less soluble in water and a somewhat better solvent for oils, waxes and resins. It is at present one of the cheapest organic solvents, and is used to some extent in the formulating of high octane gasoline. It has an octane number of 98.

n-Butyl ether, $(\text{C}_4\text{H}_9)_2\text{O}$, is likewise a recently available commercial solvent. Its almost complete insolubility in water, good solvent properties for fats, etc., chemical inertness, and higher boiling point (142.6°), might be predicted on the basis of its structure.

Di-(β -chloroethyl) ether, $(\text{CH}_2\text{ClCH}_2)_2\text{O}$, (chlorex) is a relatively new commercial solvent and finds uses in the lacquer and

textile industries, where its high boiling point (178.5°) is an advantage. It is also resistant to hydrolysis. It is made from ethylene chlorohydrin (p. 234) and large amounts are converted into divinyl ether by dehydrochlorination.

Divinyl ether, $(\text{CH}_2=\text{CH})_2\text{O}$, is an interesting substance because it resembles both ethylene and ordinary ether in structure, and like them can be used as a general anesthetic and is especially useful in short surgical operations. It is the principal constituent of "Vinethene" under which name it is marketed.

Dioxane is a cyclic di-ether which will be discussed later (p. 236). It has remarkable solvent properties for organic compounds and is miscible with water in all proportions.

Mixed ethers can be prepared by any of the general methods for preparing ethers. Ethyl butyl ether for example can be prepared by interaction between sodium ethoxide and butyl bromide, by heating ethyl sulfuric acid with butanol, or by passing a mixture of the alcohols over a heated alumina catalyst. In the latter case it would constitute only one of the ethers formed.

n-Propyl methyl ether, $\text{CH}_3\text{CH}_2\text{CH}_2\text{OCH}_3$, (Metopryl) is a new anesthetic said to be more powerful, less irritating and with less disagreeable after effects than ethyl ether.

Ethers in general when stored are likely to yield peroxides which may lead to explosions when a quantity of ether is distilled leaving a small residue. The higher ethers in some cases are more liable to this danger than ordinary ether. Before distilling any quantity, ethers should be treated with some good reducing agent such as sodium sulfite.

ETHERS

	Formula	Density	Boiling Point°	Solubility in 100 ml.		
				Water	Alc.	Ether
Dimethyl ether.....	$(\text{CH}_3)_2\text{O}$	(Gas)	-23.7	3700 cc.	v.s.	v.s.
Diethyl ether.....	$(\text{C}_2\text{H}_5)_2\text{O}$.719	35	8.3	inf.	—
Ethylmethyl ether....	$\text{C}_2\text{H}_5\text{OCH}_3$.725	10.8	s	inf.	inf.
<i>n</i> -Propyl ether.....	$(\text{C}_3\text{H}_7)_2\text{O}$.744	90.7	s	inf.	inf.
Isopropyl ether.....	$(\text{CH}_3)_2\text{CHO}$					
	$\text{CH}(\text{CH}_3)_2$.725	67.5	.65	inf.	inf.
<i>n</i> -Butyl ether.....	$(\text{C}_4\text{H}_9)_2\text{O}$.771	142.6	—	inf.	inf.
Isoamyl ether.....	$(\text{C}_5\text{H}_{11})_2\text{O}$.781	173	i.	—	inf.
Cetyl ether.....	$(\text{C}_{16}\text{H}_{33})_2\text{O}$	m.p. 55	270d.	—	—	—

HALOGEN SUBSTITUTED ETHERS

Dichloromethyl ether (sym.) $(\text{CH}_2\text{Cl})_2\text{O}$...	B.P. 105
Dibromomethyl ether (sym.) $(\text{CH}_2\text{Br})_2\text{O}$...	B.P. 150
Di-iodomethyl ether (sym.) $\text{CH}_2\text{I}_2\text{O}$	B.P. 219
Hexachlorodimethyl ether, $\text{CCl}_3\text{-O-CCl}_3$	B.P. 98 (with decomposition)
Monochloroether, $\text{CH}_3\text{CHCl-O-C}_2\text{H}_5$	B.P. 98
Trichloroether, $\text{CHCl}_2\text{CHCl-O-C}_2\text{H}_5$	B.P. 170-175
Perchloroether, $(\text{C}_2\text{Cl}_5)_2\text{O}$	M.P. 69 (decomposes on distillation)

PROBLEMS

1. Construct the structural formulas for six isomeric ethers having the molecular formula $\text{C}_5\text{H}_{12}\text{O}$. How might each be prepared?

2. In the preparation of ether by the action of sulfuric acid on alcohol, what reason is there for expecting the formation of a small amount of ethylene?

3. What would result if methyl iodide containing some water were treated with (a) metallic sodium, (b) with sodium methylate?

4. The two substances *n*-butyl alcohol and diethyl ether have the same molecular formula, $\text{C}_4\text{H}_{10}\text{O}$. How could they be distinguished by a chemical test? How could a sample of pure butyl alcohol be distinguished by chemical means from a sample containing 25 per cent of diethyl ether?

5. Glycerol which has three hydroxyl groups in its structure is not soluble in ether. Would you expect it to be soluble in alcohol?

6. If ether and water are put together, which will form the upper layer? Suppose the ether layer contains 30 per cent ethyl iodide, which layer will be uppermost? Suppose the water layer was a saturated solution of salt (density 1.20), where would you expect to find the ether-ethyl iodide layer?

7. Suppose one has on hand only 125 ml. of carbon tetrachloride with which to extract a solute from one liter of water. The solute is twice as soluble in carbon tetrachloride as in water. How will the loss in the water layer compare if on the one hand the carbon tetrachloride is used all at once or on the other hand if used in five 25 ml. portions?

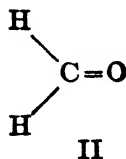
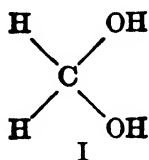
CHAPTER VII

ALDEHYDES AND KETONES

Aldehydes

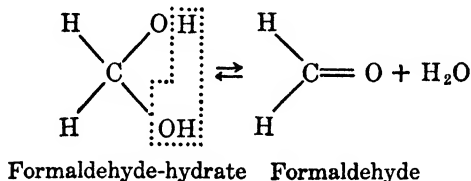
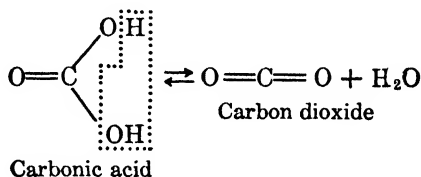
If suitable precautions are taken, the oxidation of an alcohol in solution may be stopped short of complete combustion, in which case important intermediate oxidation products may be recovered. In the case of methanol, ethanol and other primary alcohols, *aldehydes* are first formed whether the oxidation is carried out in solution or by the use of contact catalysts which cause *dehydrogenation* (loss of hydrogen). These are very easily oxidized, highly reactive, poisonous compounds. They are appreciably more volatile than the corresponding alcohols and this is an important factor making possible (in the case of the lower members) their removal from an oxidizing solution before they are themselves further oxidized.

Formaldehyde. The aldehyde obtained from methyl alcohol is called *formaldehyde*. Methanol itself is the first oxidation product of methane (p. 68). The next oxidation product should have two valences attached to oxygen, which condition is satisfied in either of the two formulas indicated below.



Formaldehyde has the molecular formula CH_2O and therefore corresponds to formula (II). The substance (I), if formed by the oxidation, loses the elements of water immediately. In fact we find that *with a few notable exceptions compounds with two hydroxyl groups attached to the same carbon atom, when formed, are unstable and dehydrate readily.*

The relationship between the two structures (I) and (II) is the same as exists between carbon dioxide and carbonic acid. In carbonic acid there are two hydroxyl groups attached to one carbon atom, but this combination is unstable, and hence carbonic acid has never been obtained other than in water solution; water readily breaks off forming carbon dioxide.



In aqueous solution, formaldehyde has very weak acidic properties, due to the presence of the hydroxyl groups in the hydrated form, but this very weakly acidic substance like carbonic acid cannot be isolated but easily passes over into its anhydride.

If methylene dichloride, CH_2Cl_2 , is caused by continued treatment to react with water, we should expect to get the substance $\text{CH}_2(\text{OH})_2$. This probably happens but as indicated above this substance breaks down readily yielding formaldehyde, CH_2O and water.

Dehydrogenation as a Mechanism of Oxidation. In the oxidation of methanol and other alcohols there is considerable evidence to indicate that the reaction actually involves a dehydrogenation.



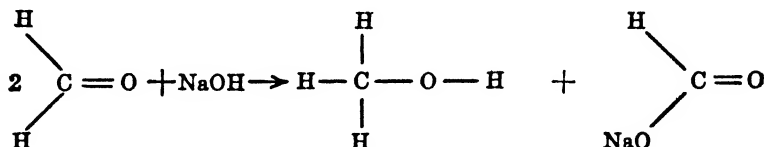
At high temperatures in the presence of catalysts hydrogen is actually eliminated as such. Under other conditions there is evidence of the dissociation and removal of hydrogen (in the presence of a suitable "hydrogen acceptor") before the hydrogen is oxidized to water. Many organic oxidations probably involve dehydrogenation; in all cases the accompanying result is the increase in the valence of the element oxidized for a non-metallic element. Some oxidations such as that of ethylene (p. 54) do not involve dehydrogenation, but the actual entrance of oxygen into the compound oxidized.

Formaldehyde is made industrially by the oxidation of methanol with air at high temperature, in the presence of copper or silver as a catalyst. The oxidation to formaldehyde is one of the important uses to which methanol is put. Formaldehyde is sold on the market principally in the form of a 40 per cent aqueous solution known as "*formalin*," of which about 450,000,000 pounds are now produced annually in America.

As a pure substance, formaldehyde is very rare, because it is a very active substance and undergoes polymerization. This consists, as indicated previously, in a reaction between molecules of the same kind to produce a substance with a molecular weight a multiple of that of the original substance. When pure formaldehyde is allowed to stand at its boiling point, -21° , it is converted into a white amorphous mass from which a solid *polymer* has been isolated, known as *trioxymethylene* (*trioxane*), which has the molecular formula $C_3H_6O_3$. Trioxane is a commercial chemical (Du Pont) used as a source of anhydrous formaldehyde because it is readily soluble in organic solvents with the exception of alkanes and it can be converted to formaldehyde at controlled rates by varying concentrations of acid catalyst. The crystals of trioxane emit light on being fractured or torn. When a water solution of formaldehyde is evaporated, a different kind of polymerization takes place and a solid substance, *paraformaldehyde* or *paraform*, results, which, unlike trioxymethylene, is insoluble in water and is of very high molecular weight. This substance when heated breaks down into formaldehyde, and for disinfecting purposes formaldehyde is frequently sold in the form of "*paraform candles*" which are burned to generate for-

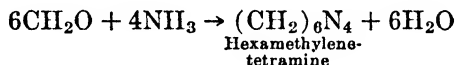
maldehyde. When formaldehyde is allowed to stand in dilute alkaline solution, it undergoes a still different type of polymerization, with the formation of a mixture of sugars known as *formose*, which will be mentioned later.

Formaldehyde undergoes several reactions which are not characteristic of the aldehydes generally. When it is treated with sodium hydroxide solution, an oxidation-reduction reaction takes place between the formaldehyde molecules, part of which are oxidized and part of which are reduced.



Many aldehydes instead of undergoing this type of reaction polymerize in the presence of strong alkalis.

With ammonia, formaldehyde forms a complex compound, *hexamethylenetetramine*, which is used as an "accelerator" in the vulcanization of rubber and in making "Bakelite." It is also used in medicine under the name "urotropine" or "methenamine."

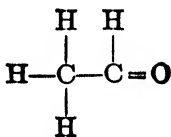


Uses of Formaldehyde. Formaldehyde reacts with protein substances which occur in tissues making them tough and insoluble, and hence is used for the preservation of specimens for study; also for embalming. The reactions involved will be mentioned later. It acts on the protein materials of a hide in a similar manner and has been used in the making of leather. Any protein material can be hardened in this way, and by use of formaldehyde threads of glue can be made into a kind of artificial silk, or casein from milk can be converted into an ivory substitute.

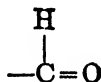
By the reaction of formaldehyde with phenol (carbolic acid) or similar substances, resinous substances are formed which with proper treatment become hard, very tough, and resistant to

chemical action. Material of this kind known as *Bakelite*¹ is not only hard and tough, but can be molded into any desired shape, is a good electrical insulator, and is resistant to chemical action. It is usually dark in color but can be produced in a form that is transparent and nearly colorless. The reactions involved in the formation of these materials are very complex and products of this kind can be made in a variety of ways. Formaldehyde is used also as a disinfectant and germicide. Various ways have been used for generating the gas, of which the method of burning paraformaldehyde candles is the most important.

Acetaldehyde. By oxidation of ethyl alcohol, a substance similar to formaldehyde is formed with the molecular formula C_2H_4O . Since this substance is similar chemically to formaldehyde, it is only reasonable to think that the atomic arrangements of the two should show a corresponding similarity. This similarity in structure is shown if this substance, acetaldehyde (äs-ët-äl'-dē-hīd), has the structure indicated below.



Acetaldehyde



Aldehyde group

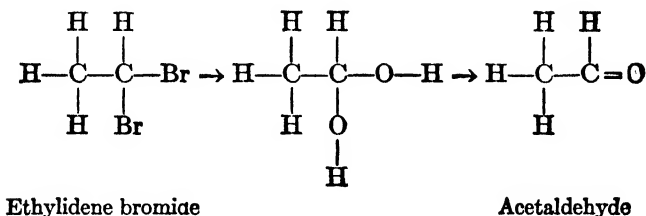
The aldehyde group (above) is then common to the two structures.

Of the two aldehydes, acetaldehyde is much less poisonous and is not therefore used as a germicide. It is less active in other ways, as for example with proteins and with phenols, and is not used so extensively as formaldehyde for making "resinoids" of the Bakelite type. Within the past few years acetaldehyde has come to be a very important chemical intermediate for the production of other chemicals. It can be made cheaply from acetylene as indicated below and many of its derivatives (including acetic acid) are used in many industries such as those

¹ Named from its discoverer L. H. Baekeland (1863-1944), a manufacturing and consulting chemist in New York. He is also the inventor of "Velox" photographic paper.

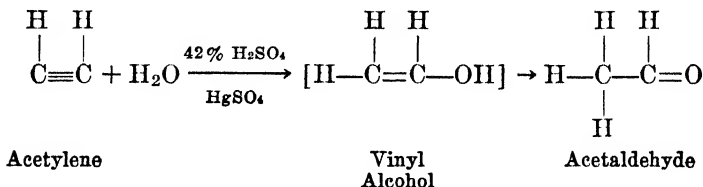
involving lacquers and rubber. During World War II acetaldehyde was used in Germany as an intermediate in the preparation of butadiene from acetylene.

Acetaldehyde may be made by the oxidation of ethyl alcohol, just as formaldehyde is made from methyl alcohol. It can also be made by the hydrolysis of *ethylidene bromide*, CH_3CHBr_2 . ($\text{CH}_3\text{CH}=\text{}$, is the ethylidene group.)



This method of formation is interesting principally because it illustrates how it is possible to differentiate between the two isomeric substances with the molecular formula $\text{C}_2\text{H}_4\text{Br}_2$. Only one of the two substances produces an aldehyde on hydrolysis, and aldehydes are easily recognized by simple tests.

Acetaldehyde is made technically from acetylene by absorbing the gas in sulfuric acid in the presence of mercury salts which act as catalysts. The reaction can be pictured as the addition of a molecule of water to acetylene forming vinyl alcohol. Vinyl alcohol is unstable and at once isomerizes almost completely to acetaldehyde (pp. 109 and 113).

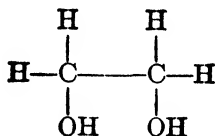


This aldehyde is formed in small amounts during alcoholic fermentation and is obtained as a by-product when the alcohol is distilled.

General Properties of Aldehydes

Oxidation. The chemical properties of the aldehydes in general may be learned from a study of acetaldehyde which is more typical of the class than formaldehyde. One of the most outstanding characteristics of the aldehydes is their ease of oxidation. Ethane, for example, is very difficult to oxidize, ethyl alcohol is much easier to oxidize, and we find in acetaldehyde a substance distinctly easier to oxidize than the alcohol. It would appear that oxidation facilitates further oxidation.

The oxidation of ethyl alcohol might proceed in two ways attacking either of the two carbon atoms. If the oxidation affects the carbon atom already holding oxygen, the product is an aldehyde (which is actually formed), whereas if the oxygen should go to the other carbon atom a di-alcohol with the structure



would be formed. A di-alcohol with this structure is known (p. 232) and is quite stable, but it is not formed by oxidation of ethyl alcohol. It is clear therefore that the carbon atom where oxygen is attached is the "vulnerable" position in the molecule.

The products formed by the oxidation of aldehydes (acids) are not themselves as easily oxidized as the aldehydes, so that in the aldehydes we have the most easily oxidized organic substances of simple type. An alkaline solution containing silver ions (ammoniacal solution) oxidizes aldehydes and the silver ions are reduced to metallic silver which deposits as a silver mirror if the glass container is clean. This may be used as a test for aldehydes. It is not, however, conclusive because some other easily oxidized substances besides aldehydes also give the same result.

Certain colors are produced when aldehydes are treated under definite conditions and these color tests are more trustworthy to show the presence of aldehydes. These colors are due to the presence of definite though often unknown compounds which are as a rule complex, and cannot be treated here.

By reason of the fact that aldehydes are so very easily oxidized, it is not generally easy to prepare them by the direct oxidation of alcohols in solution, because the conditions which will oxidize alcohols will also, of course, oxidize the more easily oxidized aldehydes. The fact that the simpler aldehydes are very volatile, however, helps make possible their preparation in this way, because the aldehydes tend to remove themselves from the oxidizing conditions as soon as they are formed, and before they are further oxidized. An acid solution of a dichromate may be used in this way to oxidize an alcohol and the high volatility of the aldehyde allows some of it to escape from the mixture before it in turn is oxidized. Vigorous stirring of the solution or forcing through a current of air increases the tendency of the aldehyde to escape and greatly increases the amount of aldehyde which can be recovered unoxidized.

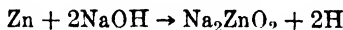
If a glowing coil of platinum wire is held in the mouth of a flask containing methyl or ethyl alcohol, the platinum wire will continue to glow due to the oxidation of the methyl alcohol vapor on the surface of the platinum by the oxygen of the air. The vapor of the alcohol and the oxygen come together on the surface of the hot platinum and by the catalytic effect of the platinum are made to react to form the products of oxidation. Vapors of the aldehyde are given off and at the same time the alcohol is in part completely burned to carbon dioxide and water. The high volatility of the aldehydes causes them to escape with great rapidity as soon as they are formed, and in this way they in part escape oxidation.

Reduction. The reverse process whereby aldehydes can be converted into primary alcohols by reduction can quite easily be carried out in the case of the simpler and more volatile aldehydes, but is not generally of much importance. Hydrogen gas in the presence of finely divided nickel held at about 140° may be used to carry out the reduction. The nickel in this case acts as a catalytic agent just as the platinum does in the experiment mentioned above.

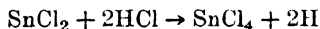
Reducing Agents. Hydrogen gas itself is seldom a reducing agent unless a catalyst is present. Platinum or palladium black makes it

effective at ordinary temperatures, while finely divided nickel as in the case just cited is very often used as a catalyst working at temperatures in the neighborhood of 200°.

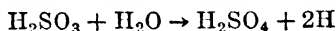
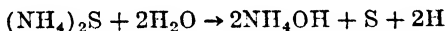
For the reduction of organic compounds, hydrogen is often liberated from some of its compounds in "nascent state." This may be accomplished by the action of metallic sodium or sodium amalgam on an alcoholic or moist ether solution of the substance to be reduced. The sodium amalgam acts less vigorously than the pure sodium because the mercury in which it is dissolved acts as a diluent. Other metals, such as zinc or iron or tin, may be used to liberate hydrogen in an acid solution of the substance to be reduced. Zinc can also be used in alkaline solution from which it liberates hydrogen and forms a zincate.



Stannous chloride in the presence of hydrochloric acid is a reducing agent.



Ammonium sulfide and sulfur dioxide and other easily oxidized substances in water solution are also used as reducing agents in various cases.

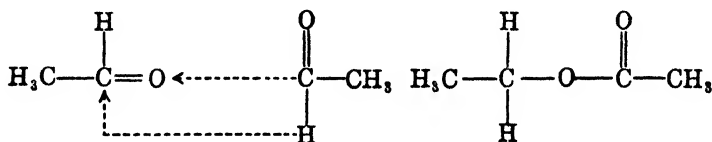


Hydriodic acid at high temperatures is one of the strongest reducing agents available for reducing organic compounds.



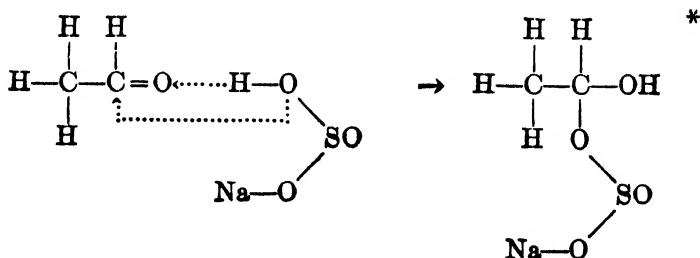
Electrolytic reduction has already been referred to (p. 81).

Intermolecular Oxidation-Reduction. In the presence of aluminum ethoxide, acetaldehyde undergoes intermolecular oxidation and reduction as does formaldehyde in the presence of alkali. Under the conditions of the experiment, however, the alcohol and acid do not appear as separate products but the ester, ethyl acetate (p. 165) is formed instead.

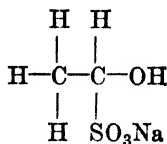


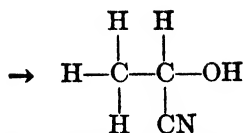
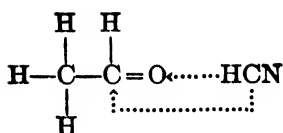
In the process one carbon atom is reduced (on the left) and another (on the right) is oxidized, since the first appears in the final product with one valence attached to oxygen and the second with three valences to oxygen. This constitutes a commercial method for preparing ethyl acetate and since this ester is usually made from ethyl alcohol and acetic acid, acetaldehyde serves as a substitute for both of these important reagents.

Other Addition Reactions. The formulas which we have tentatively given to the aldehydes show a double bond between carbon and oxygen. Though we might expect a double bond between carbon and oxygen to be somewhat different from a double bond between carbon atoms, we should expect to find a similarity. We find, in fact, that aldehydes are not only able to add hydrogen as in their reduction, but also add certain other substances, notably sodium bisulfite, hydrocyanic acid, and ammonia; also the Grignard reagents which are to be studied later. The equations for certain addition reactions of acetaldehyde are given below, while others that are more complicated are discussed in the paragraphs following.

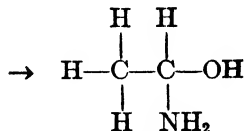
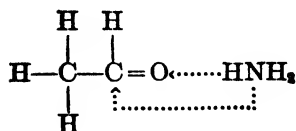


* The structural formula of the bisulfite-addition compound has never been rigorously proved. It is frequently shown with the sulfur linked directly to carbon



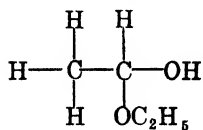


Acetaldehyde cyanohydrin

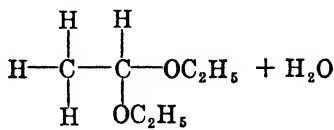
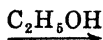
Aldehyde-ammonia
(unpolymerized form)

The ammonia addition compound pictured undergoes polymerization. It will be noted that in each case the positive hydrogen becomes attached to the negative oxygen to form a hydroxyl group, and the rest of the molecule added becomes attached to the carbon which is more positive. The addition of sodium bisulfite is made use of in the purification of aldehydes because the addition products formed are often crystalline solids which can be purified and used to regenerate the aldehydes after purification. Such a crystalline substance is much more easily purified than a liquid aldehyde. Reactions of the above types are in general reversible.

Formation of Di-Alcohol Derivatives of Aldehydes. In the presence of acids which act as catalysts, acetaldehyde (as well as other aldehydes) probably adds alcohol to form first a hemi-acetal.



Hemi-acetal

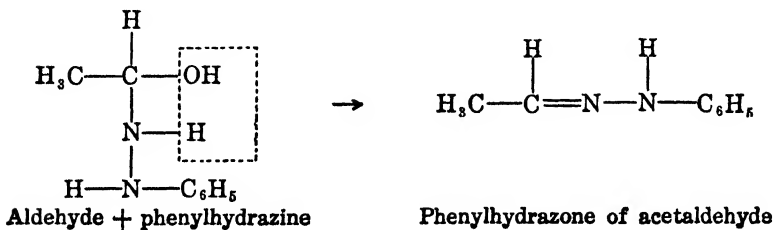
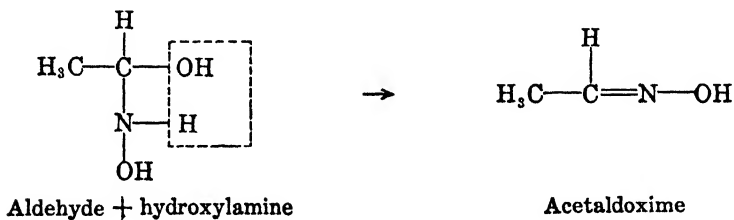


Diethyl (acetal)

The ultimate product of the reaction is a stable substance, *acetal* (äs'-ët-äl), which as the formula shows, is a di-ether or ether of a di-alcohol. The di-alcohol itself (aldehyde-water addition

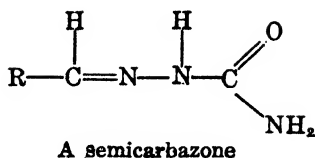
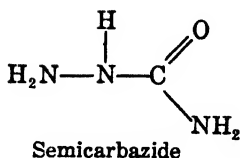
product) cannot be isolated but numerous derivatives are known including esters as well as ethers. The acetals are unlike ordinary ethers in that they undergo hydrolysis readily in the presence of acid catalysts. This may be correlated with the stronger acidic properties that di-alcohols in general possess.

Reactions with Hydroxylamine and Phenylhydrazine. The addition of ammonia to acetaldehyde has been mentioned. Two derivatives of ammonia, hydroxylamine (hī-drōk'sīl-ă-mēn), H_2NOH , and phenylhydrazine, $\text{C}_6\text{H}_5\text{NHNH}_2$, react with acetaldehyde probably in an analogous fashion, but the addition is followed by a splitting off of the elements of water from the adjacent carbon and nitrogen atoms.



These reactions are sometimes used to purify aldehydes, because the products formed are usually crystalline and they may often be more easily separated from the original impurities than the aldehyde could be. These crystalline derivatives are also frequently used to identify aldehydes.

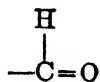
Other derivatives of ammonia are sometimes used in a similar manner and for a similar purpose. Among these is *semi-carbazide*.



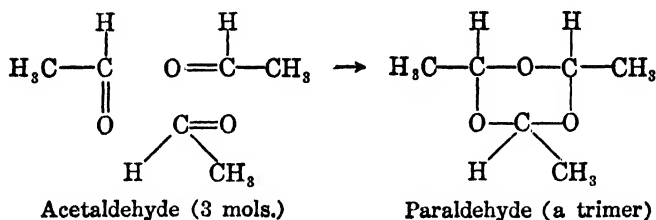
It reacts in an analogous manner and the product is called a *semicarbazone*.

Reaction with Phosphorus Pentachloride. When treated with phosphorus pentachloride, acetaldehyde acts just as though it were a di-alcohol, since two chlorine atoms become attached to the carbon atom in place of the oxygen atom, to form ethylidene chloride. The ethylidene chloride is the hydrochloric acid ester of a di-alcohol, and by its hydrolysis, as has already been stated, acetaldehyde is produced.

Polymerization is, as we have indicated, a particular type of addition reaction, in which molecules of the substance add to each other. The fact that it takes place with certain unsaturated hydrocarbons and with aldehydes emphasizes its dependence upon an unsaturated condition. Acetaldehyde polymerizes, when a small amount of concentrated sulfuric acid is brought in contact with it, into *paraldehyde*, $\text{C}_6\text{H}_{12}\text{O}_3$, each molecule of which is equivalent to three molecules of aldehyde. It is a liquid which can be reconverted into acetaldehyde by heating it with dilute sulfuric acid. The structure of paraldehyde and the method by which it may be formed from three molecules of acetaldehyde are indicated below. It will be noted that as the substance polymerizes, the double bonds disappear and that the polymer is not an aldehyde since it does not contain the group

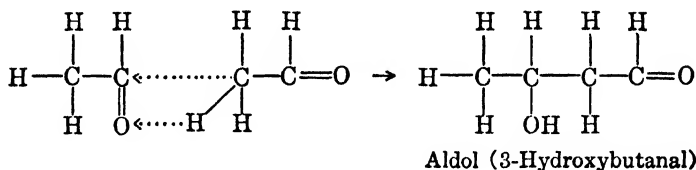


which is characteristic of aldehydes.

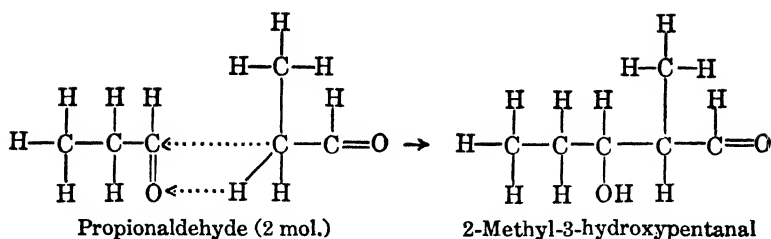


When acetaldehyde is kept at low temperature in the presence of acids, an isomeric polymer, $\text{C}_6\text{H}_{12}\text{O}_3$, called *metalddehyde* is formed. A tetramer $\text{C}_8\text{H}_{16}\text{O}_4$ can also be formed. These substances can also be converted into acetaldehyde by continued heating. In the presence of strong bases acetaldehyde changes into a yellow resinous material of unknown nature which is thought to be a polymer or a mixture of polymers of aldehyde, and is called *aldehyde resin*. This material is not convertible into aldehyde like the other polymers mentioned.

Finally, if acetaldehyde is allowed to stand in weak alkaline solution, an addition reaction takes place according to the following:



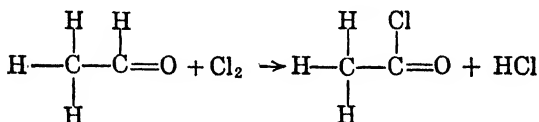
The substance formed is both an aldehyde and an alcohol and is accordingly called *aldol*, and this reaction and other reactions which are similar to it are termed "*aldol condensations*." The term *condensation* is applied particularly to reactions in which carbon atoms become joined together. In this addition reaction a hydrogen atom becomes attached to oxygen, and carbon becomes attached to the carbon of the unsaturated carbonyl ($\text{C}=\text{O}$) group. If we deal with a higher aldehyde such as *propionaldehyde*, the reaction proceeds thus:



Only a hydrogen atom which is attached to a carbon atom next to the carbonyl group is capable of breaking away in an addition reaction of this kind. The tendency toward reactivity residing in the carbonyl group is transmitted to neighboring C-H linkages. This phenomenon is to be observed repeatedly in carbonyl compounds.

Aldol condensations are in general reversible.

Reactions with Halogens. If pure acetaldehyde is treated with chlorine gas, the hydrogen attached to the carbonyl group may be replaced.

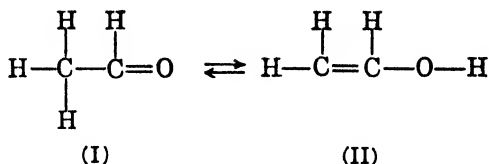


This reaction, however, is relatively of little importance. When acetaldehyde in weakly alkaline solution is treated with chlorine the reaction takes quite a different course, and chloroform, CHCl_3 , is formed according to the equation:



Under similar conditions treatment with bromine produces bromoform, CHBr_3 , and iodine produces iodoform, CHI_3 . From the standpoint of structure, it is difficult to see how chlorine could act to produce chloroform from a substance with the structure which we have assigned to acetaldehyde.

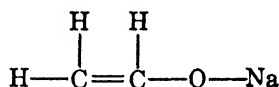
The reactions of acetaldehyde with the halogens are rationally explained if acetaldehyde is assumed to be a mixture of the two substances represented below, in equilibrium.



Either substance may change to the other by the shifting of hydrogen from carbon to oxygen, or vice versa. Such a change as this may take place spontaneously in both directions maintaining an equilibrium.

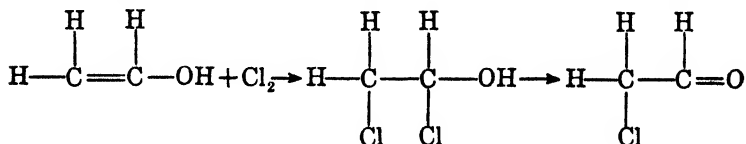
The change from (I) to (II) is similar to that which takes place in the aldol condensation. The C-H bonds in the methyl group are weakened by the influence of the carbonyl group, and an addition to the carbonyl group takes place within the one molecule. The change from (II) to (I) consists of an *intramolecular* addition of an alcohol to a C=C linkage.

Alkali, if present, will react with component (II), because of its acidic character, forming the substance



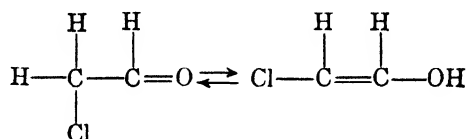
and this will decrease the amount of component (I) in the mixture.

If such an equilibrium mixture as we have been describing is treated with chlorine, the chlorine will be added by component (II) which has doubly bonded carbon atoms in its structure, because, as we have already noted, addition reactions of this kind are much faster and take precedence over substitution reactions.

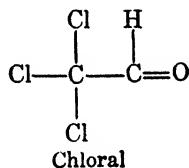


We have also noted (p. 80) that when a chlorine atom and a hydroxyl group become attached to the same carbon atom, the combination is unstable and hydrogen chloride breaks off. This reaction is especially favored by the presence of the alkali which

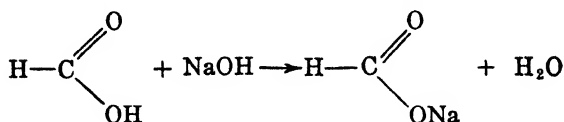
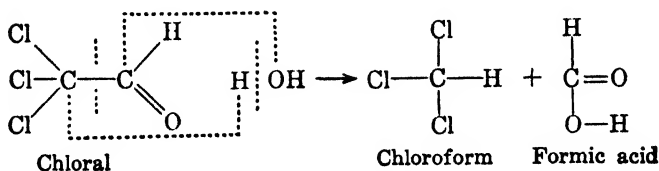
immediately neutralizes the acid. By this reaction there is formed a chlorine substituted aldehyde, which like acetaldehyde itself should exist in two forms as indicated:



This unsaturated form may then add on another molecule of chlorine, followed by a breaking off of a molecule of hydrogen chloride, and the formation of dichloroacetaldehyde. The process may then repeat and form trichloroacetaldehyde. When acetaldehyde is treated with chlorine under these conditions, *trichloroacetaldehyde* or *chloral* (kló'rál) is actually formed, and



from it, by heating in alkaline solution, chloroform is obtainable. The formation of chloroform from chloral is most simply pictured as a hydrolysis reaction influence by the alkali, followed by a neutralization of the formic acid by the alkali, as indicated.



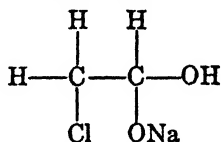
The formic acid and sodium formate pictured in these equations will be studied later. Carbon-carbon linkages such as are present

in ethane are very stable. Whenever the carbon atoms become loaded with non-metallic atoms such as chlorine or oxygen, the linkage is greatly weakened, and alkalis are especially effective agents in bringing about a hydrolytic splitting such as occurs in chloral (or even in analogous compounds containing more hydrogen).¹

It is thus possible, by means of the assumption that acetaldehyde exists in two forms in equilibrium, to explain rationally the formation of chloroform under the conditions used. Exactly the same explanation serves for the formation of bromoform and iodoform when bromine and iodine, respectively, are used. While the assumption that acetaldehyde is a mixture of two isomers in equilibrium may seem unusual, a similar condition is met often even in inorganic chemistry. It is not always possible to picture completely the properties of a substance by the use of a single formula. For example, the properties of a solution of hydrogen sulfide in water cannot be depicted by assuming either that the substance exists wholly in the form of H^+ ions and S^{--} ions, or that it exists wholly as undissociated H_2S . Rather, it is thought of as an equilibrium mixture of H^+ ions, SH^- ions, and S^{--} ions, and undissociated H_2S .

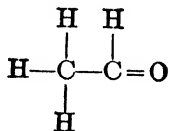
The assumption that acetaldehyde exists partly in the form of an unsaturated alcohol is strengthened by the fact that acetaldehyde reacts with metallic sodium, liberating hydrogen in a manner characteristic of alcohols. Furthermore, there is no separate substance known which has the structure corresponding to this unsaturated alcohol and attempts to prepare it have led to the formation of the substance which we know as acetaldehyde.

¹ An alternative interpretation of this "chloroform reaction" may be made in terms of sodium hypochlorite as the active agent instead of chlorine. In this case the first addition product is



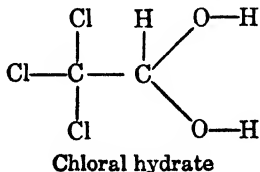
which decomposes to give chloraldehyde. The successive reactions may follow in an analogous manner.

Notwithstanding the fact that acetaldehyde probably has two structures, the formula



the one commonly used for it because the substance in the pure form and in the absence of alkalis is almost entirely in this form, and this formula explains the majority of the reactions. The unsaturated alcohol form of the aldehyde is called the *enol* (unsaturated alcohol) form. It is sometimes named vinyl alcohol as though it were an independent substance. ($\text{CH}_2=\text{CH}$ is the vinyl group.) Such an equilibrium condition between isomers, as is illustrated by this case, is spoken of as *tautomerism* and the different structures concerned are called *tautomers* or *tautomeric* forms. Many cases of tautomerism have been well established, and in the more common cases one form changes over into the other tautomer merely by the shifting of the position of a hydrogen atom, which is the lightest of atoms and the most mobile. These tautomeric changes are often very rapid.

Chloral, CCl_3CHO , represents an example of a substituted aldehyde, and substituted aldehydes retain the characteristics of ordinary aldehydes though in some cases they are noticeably modified by the presence of other atoms or groups in the compound. Thus chloral reduces alkaline silver solution, forms addition products and polymerizes like the other aldehydes. In contrast to other aldehydes, however, chloral adds on water to give a rather stable compound *chloral hydrate* with the structure:



This substance has faint acid properties and affects indicators. It is a little weaker than hydrocyanic acid. Other aldehydes, it

will be recalled, also react in the same way with water but not to any great extent and the products are not stable and are not distinctly acid. The chlorine in the molecule increases the tendency to ionize as an acid, as is also shown by other cases to be cited later. Chloral hydrate has stronger acid properties than the hydrates of other aldehydes, and chloral itself is thus the anhydride of a more strongly acidic substance, and is more reactive with water, as might be predicted from the consideration of this fact. Chloral is made by the action of chlorine on ethyl alcohol.

Higher Aldehydes. There is comparatively little more to be learned about the general properties of aldehydes by a study of the higher homologs. Most of the discussion regarding acetaldehyde applies to other members of the series as their general reactions are similar. A long series of these aldehydes is known, and show a gradation in chemical properties, becoming, as the length of the carbon chain increases, more like hydrocarbons and less like formaldehyde. The higher members, for instance, are less easily polymerized. There is also a gradation in physical constants, solubility, etc., just as in the case of other homologous series already considered.

ALDEHYDES

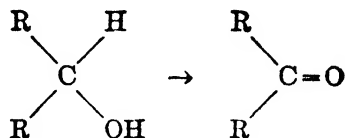
	Formula	Boiling Point	Solubility in 100 parts		
			Water	Alc.	Ether
Formaldehyde (methanal)	HCHO	-21	s.	s.	s.
Acetaldehyde (ethanal)	CH ₃ CHO	20.8	inf.	inf.	inf.
Propionaldehyde (propanal)	CH ₃ CH ₂ CHO	48.8	20 (20°)	"	"
n-Butyraldehyde (butanal)	CH ₃ (CH ₂) ₂ CHO	75.7	3.7	"	"
iso-Butyraldehyde (2-methylpropanal) ..	(CH ₃) ₂ CHCHO	61	11	"	"
n-Valeraldehyde (pentanal)	CH ₃ (CH ₂) ₃ CHO	103.7	sl.s	—	—
iso-Valeraldehyde (2-methylbutanal) ..	(CH ₃) ₂ CHCH ₂ CHO	92.5	sl.s	s.	s.
Stearaldehyde (octadecanal)	C ₁₇ H ₃₄ O	212 (22mm.)	i.	—	sl.s.

Nomenclature. Aldehydes are named using the suffix *al* to replace the final *e* in the name of the hydrocarbon from which they are derived. When the aldehyde is named from the common name of the corresponding acid the "ic" is dropped from the acid name and "aldehyde" is added (CH_3CHO , acetaldehyde, ethanal).

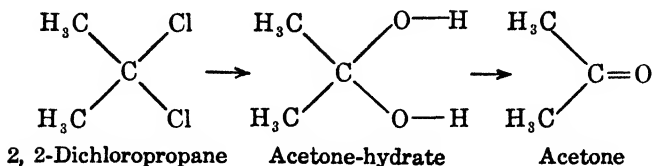
Ketones

The success of the student in grasping the important features of the study of organic chemistry will depend to a large extent upon his ability, not to learn isolated facts, but rather to correlate the new material with what has already been presented. Nowhere does the desirability of correlation become more apparent than in the study of the ketones which resemble the aldehydes in many respects, and show definite differences which appear perfectly reasonable in the light of our previous study.

Formation of Ketones by Oxidation of Secondary Alcohols. The secondary alcohols, it will be recalled, have only one hydrogen atom attached to the carbon atom holding the hydroxyl group. Since oxidation follows at the point where oxygen is attached, the next stable product will be the one indicated below.

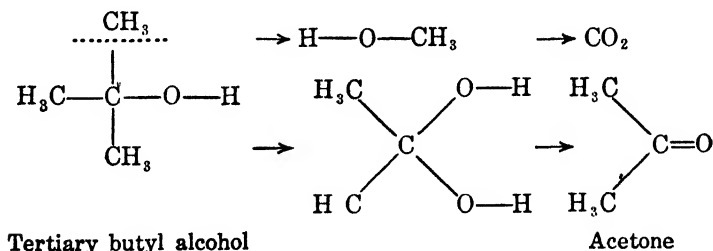


The substance formed differs from the aldehydes in structure in that no hydrogen is attached to the carbon atom which holds the oxygen. It contains the *carbonyl group*, $\text{C}=\text{O}$, which is a part of the aldehyde group. Insofar as the reactions of the carbonyl group are concerned, aldehydes and ketones are much alike. The structure of acetone, the simplest of the ketones, is established by the fact that it can be made by the oxidation of isopropyl alcohol, in accordance with the formulas given above, and can also be obtained by the hydrolysis of 2,2-dichloropropane.



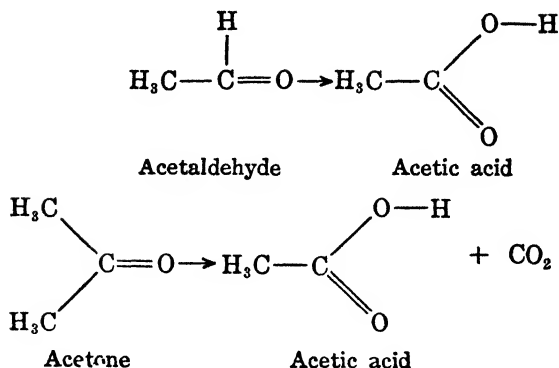
The structure given is also in accord with the chemical properties as further discussion will make clear.

Formation of Ketones by the Oxidation of Tertiary Alcohols. It is characteristic of the tertiary alcohols that the carbon atom holding the hydroxyl group holds no hydrogen atoms. No more oxygen can become attached to the carbon atom already holding the hydroxyl group without breaking a bond between two carbon atoms. For this reason, because the carbon-carbon bonds are difficult to break, the tertiary alcohols are not as easily oxidized as the primary or secondary alcohols. In this case as in others the oxidation proceeds on the carbon atom already holding oxygen.



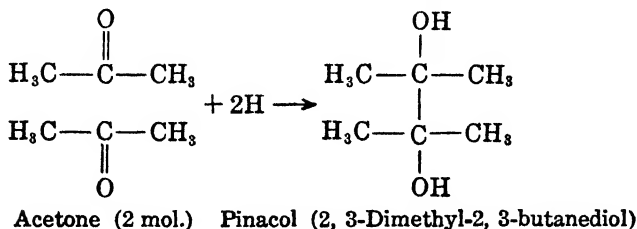
By the breaking off of the methyl group, methyl alcohol is probably first formed, and is oxidized further possibly to carbon dioxide depending on the oxidizing conditions. The rest of the molecule goes to form the ketone.

Lesser Ease of Oxidation of Ketones. The outstanding difference between the aldehydes and the ketones is the fact that ketones are not so easily oxidized. This can be attributed to the difference in structure. In aldehydes, a hydrogen atom attached to the carbon of a carbonyl group may be replaced by a hydroxyl group, whereas in ketones a carbon-carbon linkage must be broken if the oxidation is to proceed on the same carbon atom.



As a result of this difference in ease of oxidation, aldehydes and ketones may be easily distinguished. Simple ketones do not give the silver mirror test. In ketones (and tertiary alcohols as well) in which there are different alkyl groups attached to the carbon already holding oxygen, the larger alkyl groups are usually the first to be broken off by oxidation.

Reduction of Ketones. Ketones like aldehydes may be reduced by the action of nascent hydrogen or by hydrogen gas in the presence of a copper or nickel catalyst. In the case of ketones reduction produces secondary alcohols by addition of hydrogen at the double bond of the carbonyl group. These reactions are frequently accompanied by more complicated reactions such as the formation of *pinacol* as illustrated below.

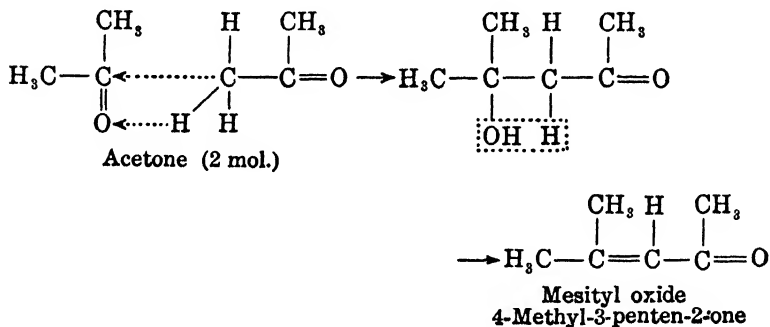


The term "pinacol" is simply a special name applied to this type of di-alcohol.

Other Addition Reactions. As would be expected from the presence of the carbonyl group in the structure, ketones are able, like the aldehydes, to add certain reagents. The highly

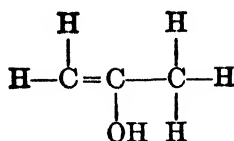
unstable di-alcohol formed by the addition of a molecule of water, and the reduction by addition of hydrogen have been mentioned. The reactivity of the carbonyl group is altered by the absence of the attached hydrogen, and ketones do not form simple addition products with ammonia, and do not polymerize as the aldehydes do. Ketones, like the aldehydes, add hydrocyanic acid, the Grignard reagents, and often sodium bisulfite. They also react with hydroxylamine and phenylhydrazine in a manner strictly analogous to the behavior of aldehydes. The products are known as *ketoximes* and *phenylhydrazones* respectively.

Acetone molecules also add on to each other reversibly in the presence of alkali to give a substance analogous to aldol. At higher temperatures this substance loses the elements of water spontaneously and becomes unsaturated in a manner analogous to the behavior of ethyl alcohol under strong dehydration (p. 79).



With phosphorus pentachloride ketones react like the aldehydes.

Reaction with Halogens in Alkaline Solution. Acetone like acetaldehyde yields iodoform when its weakly alkaline solution is treated with dilute iodine solution. Since iodoform has a characteristic appearance and odor, this reaction is used as a qualitative test, as explained later. Chloroform or bromoform can be made from acetone just as from acetaldehyde. These reactions like the analogous reactions of acetaldehyde are not easily explained upon the basis of the ordinary formula. However, acetone like acetaldehyde reacts with metallic sodium liberating hydrogen (like an alcohol) and it is thought to exist in the tautomeric form.



Acetone (enol form)

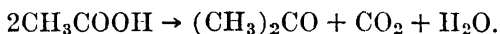
This substance, as in the analogous case of acetaldehyde, evidently adds iodine, breaks off hydrogen iodide, changes to the enol form, adds iodine again, etc. The product formed other than iodoform (or bromoform or chloroform) is sodium acetate instead of the sodium formate which is formed when alcohol or acetaldehyde is used. The unsaturated alcohol corresponding to the formula given above, as an independent substance, is not known and attempts to prepare it lead to the formation of acetone just as attempts to prepare vinyl alcohol ($\text{CH}_2=\text{CHOH}$) lead to the formation of the substance known as acetaldehyde.

Ethyl alcohol (but *not* methyl alcohol), acetaldehyde, acetone and all other ketones containing the CH_3CO (acetyl) group, give the iodoform test. All alcohols, which on oxidation yield aldehydes or ketones with the acetyl group in their structure, also produce iodoform when treated with iodine and alkali. The alcohols which give the test are first oxidized to aldehydes or ketones by the iodine (or hypoiodite). These facts are all in accord with the formulation of this reaction as discussed earlier in this chapter, and one can predict on the basis of these considerations whether or not a given compound may yield iodoform.

If one is certain that other substances giving the test are absent, the formation of iodoform can be used as a test either for alcohol or for acetone, etc. Alcohol and acetone react at unequal rates and may be differentiated by careful control of the temperature.

Production and Uses of Acetone. Acetone is the most important ketone and finds important uses as a solvent. It was formerly prepared exclusively by the dry distillation of calcium acetate (p. 139) obtained from wood distillation. During World War I it was in great demand, and other means of pro-

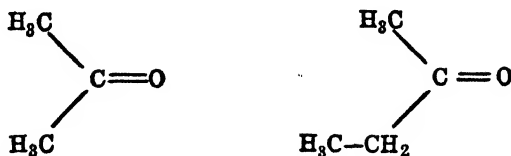
duction were developed. It was made from glacial acetic acid which was passed over heated lime and magnesia which act as catalysts.



The intermediate formation of acetates takes place under the conditions used. More recently MnO has been used as a catalyst and yields excellent results. Another method was also developed which has become an important source of acetone. A corn mash is fermented with an anaerobic organism, and the products of the fermentation are distilled. The distillate contains about 30 per cent acetone, nearly twice this amount of normal butyl alcohol (butanol) and about 10 per cent ethyl alcohol. Acetone is now made by the dehydrogenation of isopropyl alcohol over metallic copper at about 300° .

Acetone is principally used as a solvent in the production of cellulose plastics, smokeless powders, lacquers, paint and varnish removers, etc., but is also used as a raw material for the manufacture of chloroform, methacrylate resins, ketene and other valuable chemicals.

Higher Ketones. The ketones form a homologous series which show the same gradations of properties shown by other homologous series. The ketones may be either simple ketones like acetone (dimethyl ketone) or mixed ketones like methyl ethyl ketone, in which two different alkyl groups are attached to the carbonyl group.



Ketones systematically derive their names from the corresponding hydrocarbons by changing the final "e" to *one*. Acetone is propanone, methyl ethyl ketone is butanone, etc. The position of the carbonyl group where necessary is indicated by a number. Thus diethyl ketone is 3-pentanone, and methyl

propyl ketone is 2-pentanone. The naming of mesityl oxide (p. 118) illustrates a more complex case in which the number nearest the significant ending designates the position of the particular group.

SIMPLE KETONES

	Formula	Density	Boiling Point	Solubility in		
				Water	Alc.	Ether
Acetone	$\text{CH}_3\text{COCCH}_3$.792 (20°)	56.5	inf.	inf.	inf.
Diethyl ketone	$(\text{C}_2\text{H}_5)_2\text{CO}$.814 (20°)	101.7	s.	inf.	inf.
Dipropyl ketone	$(\text{C}_3\text{H}_7)_2\text{CO}$.821 (15°)	144.2	i.	inf.	inf.
Di-isopropyl ketone	$[(\text{CH}_3)_2\text{CH}]_2\text{CO}$.806 (20°)	123.7	—	—	—
Stearone	$[\text{CH}_3(\text{CH}_2)_{10}]_2\text{CO}$.798 (15°)	M.P. 88.5	i.	v.sl.s.	v.sl.s.

MIXED KETONES

Methyl ethyl ketone	$\text{CH}_3\text{COC}_2\text{H}_5$.805 (20°)	79.5	s.	inf.	s.
Methyl propyl ketone	$\text{CH}_3\text{COC}_3\text{H}_7$.812 (15°)	102	v.sl.s.	inf.	inf.
Methyl iso-propyl ketone	$\text{CH}_3\text{COCH}(\text{CH}_3)_2$.805 (15°)	93	v.sl.s.	inf.	inf.
Ethyl propyl ketone	$\text{C}_2\text{H}_5\text{COC}_3\text{H}_7$.818 (18°)	124	v.sl.s.	inf.	inf.
Ethyl isopropyl ketone	$\text{C}_2\text{H}_5\text{COCH}(\text{CH}_3)_2$.830 (0°)	114.5	v.sl.s.	v.s.	inf.
Methyl ethyl acetone	$\text{CH}_3\text{COCH}(\text{C}_2\text{H}_5)\text{CH}_3$.818 (15°)	118	sl.s.	inf.	inf.
Methyl isobutyl ketone	$\text{CH}_3\text{COC}_4\text{H}_9$.803 (19°)	116	i.	inf.	inf.
Methyl isoamyl ketone	$\text{CH}_3\text{COC}_5\text{H}_{11}$.818 (17°)	144	v.sl.s.	inf.	inf.
Methyl hexyl ketone	$\text{CH}_3\text{COC}_6\text{H}_{13}$.820 (15°)	172.5	i.	inf.	inf.
Methyl nonyl ketone	$\text{CH}_3\text{COC}_8\text{H}_{17}$.829 (18°)	224	i.	s.	s.
(Chief constituent oil of rue)						
Ethyl heptadecyl ketone	$\text{CH}_3\text{COC}_{17}\text{H}_{35}$.811 (55°)	266.5 (at 110 mm.)	i.	v.sl.s.	inf.

Methyl ethyl ketone and other higher ketones are widely used as solvents. Diacetyl ($\text{CH}_3\overset{\text{OO}}{\underset{|||}{\text{C}}}\text{CCCH}_3$) is used to color and flavor butter and butter substitutes.

PROBLEMS

1. What is the least number of carbon atoms that could exist in (1) a ketone, (2) a secondary alcohol, (3) a primary alcohol, (4) a tertiary alcohol, and (5) an enol.

2. The available chlorine in a sample of bleaching powder is 67 per cent. How much bleaching powder according to the equations would be necessary to convert 9 grams of acetone into chloroform? How much chloroform would it theoretically be possible to obtain?

3. How can acetaldehyde be prepared starting with acetylene and hydrogen bromide?

4. Write structural formulas for three ketones and four aldehydes all with the molecular formula $\text{C}_5\text{H}_{10}\text{O}$. Which of these compounds will give the iodoform test?

5. How could a simple aldehyde and a simple ketone be most easily distinguished?

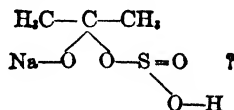
6. Suppose you were given a sample of gasoline containing an alcohol, what simple method could you use to tell approximately the amount of alcohol present? Would the same method suffice to tell the amount of alcohol dissolved in an aldehyde?

7. Write the formula for a ketone which should not be expected to exist in an enol form.

8. Suppose an aldehyde polymerized and after polymerization remained in solution. How would the freezing point of the solution be affected by the polymerization?

9. How much *sec.* butyl alcohol could theoretically be obtained from one mole of methyl ethyl ketone? How much iodoform?

10. Might the acetone bisulfite compound have the structure



Would a substance with this formula be stable in the presence of water?

11. Ethylidene chloride yields acetal when treated with the appropriate reagent. What reagent may be used?

12. The addition of sodium bisulfite to ketones with large branched chains is very slow. What reason can be given for this behavior?

13. Diacetonecamine $C_6H_{13}NO$ is formed by the interaction of acetone and ammonia. Write a probable structural formula.

14. Acetone and acetaldehyde together may theoretically undergo "aldol condensation" to yield four different products. Write their formulas. How many products could acetone and trimethyl acetaldehyde ($C(CH_3)_3CHO$) yield under the same conditions?

15. An aldol condensation may be pictured as the addition of an aldehyde to an enol. Indicate how this may be done.

16. Butanol may be produced from aldol by dehydration and hydrogenation. Picture the reactions.

17. Work out a possible structural formula (containing rings) for hexamethylenetetramine. Hint: Attach each carbon atom to two different nitrogen atoms.

18. The ozonide of ethylene yields (with water) two molecules of formaldehyde plus one of hydrogen peroxide. Write the formula of an alkene which in an analogous reaction would yield acetone, acetaldehyde and hydrogen peroxide.

CHAPTER VIII

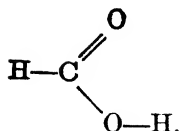
ACIDS

It has already been pointed out that not only water, but the alcohols and the aldehydes and ketones in solution have faint acidic properties. The term "acid" is, however, not ordinarily applied to such substances, but is reserved for those substances which show the acid property very distinctly. An acid (as the term is ordinarily used) affects indicators, usually has a sour taste, and forms salts which are at least moderately stable in water solution. The substances which have so far been studied do not possess these properties.

Complete oxidation of organic compounds results in the formation of carbonic acid which is an unstable acid and breaks down into water and its anhydride, carbon dioxide. However, by the incomplete oxidation of many organic compounds stable acids are formed. If formaldehyde, for example, is oxidized incompletely, a distinctly acid substance is formed which has the molecular formula CH_2O_2 . This acid is known as **formic acid** due to the fact that it was early obtained by the distillation of the bodies of red ants (Latin *formica*, an ant). It is not responsible, as is commonly supposed, for the pain caused by the stings of bees and similar insects. (Complex toxins probably of protein nature are involved.)

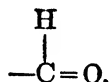
Formic acid may also be obtained by the oxidation of methyl alcohol, in which case formaldehyde is the intermediate product. However, formic acid itself is quite easily oxidized so the preparation by this means is not practicable. Methods by which it may be prepared will be given later.

For the neutralization of one mole (46 grams) of formic acid one mole of sodium hydroxide is required. Formic acid is therefore a mono acid. The simplest structure formula is



in which the right hand portion, $-\text{COOH}$, is the *carboxyl* group. This corresponds to a mono acid, since there is only one hydroxyl group and only one hydrogen atom which would be expected to ionize. Hydrogen atoms generally do not ionize away from carbon appreciably.

It will be noted that the formula pictures formic acid as having in its structure the same group we have previously found to be common to the aldehydes, *i.e.*,

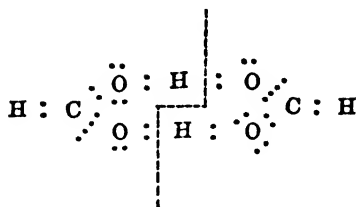


In conformity with this, formic acid in contrast to all other members of the series shows some of the characteristics of the aldehydes. It is easily oxidized; in fact, gives the silver mirror test (faintly). Formic acid, however, is unlike the other simpler aldehydes in that it does not polymerize or enter into typical addition reactions under ordinary conditions. Evidently the aldehyde group if present in formic acid is considerably modified in its properties either because of its attachment to the $-\text{OH}$ group or for other reasons.

There are interesting and somewhat complicating facts regarding formic acid which apply also to the other members of the series. They are as follows: (1) Formic acid exists in the vapor state as a mixture of single and double molecules CH_2O_2 and $\text{C}_2\text{H}_4\text{O}_4$; (2) While formic acid (and others) is commonly

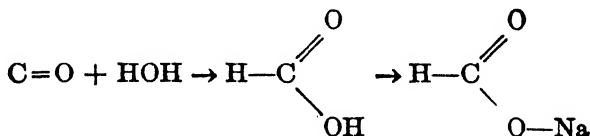
pictured as containing the $\begin{array}{c} \diagdown \\ \text{C}=\text{O} \\ \diagup \end{array}$ group it resists reduction and does not enter into the addition reactions common to this group. The failure of formic acid to act like a typical aldehyde is related to this latter fact.

Physical studies have indicated that formic acid dimer has the structure represented electronically below,



in which the two monomers (CH_2O_2) are joined together by *hydrogen bridges*. The dotted line indicates the position at which the "complex" may split. Previously we have mentioned the "acceptance" of a proton by oxygen (p. 76). According to the picture above, the upper right oxygen, for example, has "accepted" a proton *along with its oxygen attachment*, and has furnished both electrons for the connecting link between itself and the hydrogen. Further examples of this type of valence will be presented later (p. 188). This picture helps to explain both facts cited above, since this type of union would be expected to modify unsaturated (and aldehydic) properties.

Formic acid may be prepared from carbon monoxide (which is in a sense its anhydride) inasmuch as carbon monoxide is unsaturated and adds on an alkali at about 150° under pressure to give a salt of formic acid. The reaction may be conveniently pictured as taking place in two stages; first, by the addition of water to the bi-valent carbon; second, by the immediate neutralization of the acid by the alkali present.



This is used as a technical method for the production of formates because of the cheapness of the raw materials. It will be recalled that carbon monoxide is made by the interaction of carbon and water at high temperature.



For laboratory preparation formic acid can be made by heating oxalic acid (p. 246) and glycerol (p. 238). The former de-

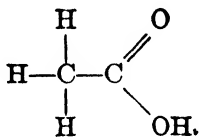
composes into formic acid and carbon dioxide while the latter acts as a catalyst. This method is not practically valuable since oxalic acid is too expensive, being itself made technically from the formate prepared as indicated above (p. 247).

Salts of formic acid may also be prepared by the action of alkali solutions on chloroform.



This illustrates the fact that the various halogen substitution products of methane react alike with alkali, whether they are mono, di-, tri-, or tetra-substitution products.

Structure and Properties of Acetic Acid. By the oxidation of acetaldehyde, the familiar acetic acid is formed. Acetic acid is much more difficult to oxidize than acetaldehyde, so it is not difficult to stop the oxidation at this point. The structural formula of acetic acid by analogy is



This represents a molecule in which one of the hydrogen atoms is differently situated than the others. This property of acetic acid is shown by the fact that only one of the hydrogen atoms is replaceable by metals. To show this the formula is sometimes written $\text{HC}_2\text{H}_3\text{O}_2$. This formula does not, however, show the relations of the other atoms in the molecule. Three of the hydrogen atoms in the structural formula are situated alike and are attached to carbon in the same way as they are in methane. This arrangement is shown to be present in acetic acid by the fact that one, two, or three of the hydrogen atoms of the acid can be replaced by chlorine just as in methane.

By treatment of acetic acid with phosphorus trichloride, chlorine takes the place of the hydroxyl group forming a compound CH_3COCl . All substances which have hydroxyl groups react in this way with either phosphorus trichloride or phosphorus pentachloride. The structural formula for acetic acid is

thus well established except for the qualification that the $\begin{array}{c} \diagup \\ \text{C}=\text{O} \\ \diagdown \end{array}$ group pictured in the formula does not behave like a typical carbonyl group.

Pure acetic acid, practically free from water, is called *glacial* acetic acid, because it freezes at about 17° and thus is often solid under ordinary conditions. Vinegar is essentially a dilute water solution of acetic acid, though there are other substances present which give it color and flavor.

Manufacture of Vinegar. There are three principal types of vinegar, spirit vinegar, cider vinegar and malt vinegar, named in the order of their importance. Spirit vinegar is made from "low wine," which is a distilled product containing about 12 per cent alcohol. Unless artificially colored, vinegar produced in this way is colorless. Cider vinegar is made from fermented apple juice which is not distilled before conversion into vinegar and hence contains coloring and flavoring matter from the fruit. Malt vinegar is made from fermented cereal infusions, and also contains coloring matter from the grain.

The most important source of spirit vinegar is molasses, and the vinegar is very often a by-product of the manufacture of yeast. One hundred gallons of molasses may yield 200-230 gallons of 10 per cent spirit vinegar. The low wine is mixed with vinegar and allowed to pass through a vinegar generator, from which is obtained vinegar containing practically no alcohol. A standard vinegar generator such as is in common use is a wooden tank 3-4 feet in diameter and 8-10 feet high. It is almost filled with beechwood shavings, corncobs, or in some cases charcoal. These materials are impregnated with microorganisms (*Mycoderma aceti*) which bring about the oxidation of the alcohol. The oxygen for the oxidation is supplied by the air which enters at the bottom of the generator and because of the heat generated by the oxidation rises and leaves at the top of the generator. A generator of this size and type is able to produce 5-8 gallons of 10 per cent spirit vinegar in 24 hours. Instead of many small generators such as mentioned above the tendency is now towards the building of much larger generators.

The bacteria which bring about the oxidation work most efficiently in a medium which contains perhaps 8 per cent acetic acid but the organisms cannot function after the acetic acid content has reached more than about 12 per cent. By proper care the conversion of alcohol into acetic acid may be practically complete.

Concentrated acetic acid is not produced from vinegar. "Pyrolygneous acid" formed by the dry distillation of wood owes

its acid properties principally to its high content of acetic acid and serves as one source of concentrated acid.

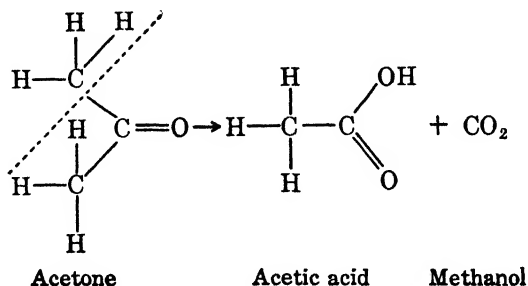
The two main industrial processes for the production of pure acetic acid are the hydration of acetylene to acetaldehyde (p. 100) followed by oxidation and the air oxidation of ethyl alcohol over a metal catalyst. Concentrated acetic acid is used extensively in the rayon and cellulose plastic industries and has numerous other uses. The sodium salt of monofluoroacetic acid, **1080**, (CH_2FCOONa) is a powerful rodenticide.

The esters of acetic acid are very important solvents (p. 175). Ethyl acetate is produced in large quantities from vinegar and "high wines" (ca. 50 per cent alcohol) from fermentation.

Formic and acetic acids are the first two members of a homologous series of acids whose formulas may be constructed, as in the cases of other homologous series, by substituting methyl groups in the formulas for the hydrogen atoms which are attached to carbon.

Formation of Acids by Oxidation of Ketones. By oxidation of primary alcohols, aldehydes are first formed, then acids. When either secondary or tertiary alcohols are oxidized, ketones result; in the case of the tertiary alcohols the ketone formed as one of the products has a lesser number of carbon atoms than the original alcohol.

By the oxidation of ketones, acids also result but the acid formed by oxidation has fewer carbon atoms than the original ketone. The carbon atom which already holds oxygen becomes attached with a third valence to oxygen, which means that one of the carbon-carbon linkages in the ketone is broken

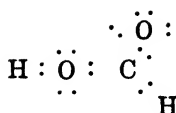
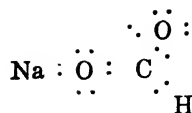


Thus in the progressive oxidation of any alcohol, *the oxidation proceeds on the carbon already holding the oxygen, until three of the valences are attached to oxygen, even though carbon-carbon linkages must be broken.* This is ordinarily as far as the oxidation will go on one carbon atom as in the next step either the adjacent or the second carbon atom is attacked.

Reactions of the Acids. Formic acid, the first member of the formic acid series (also called the fatty acid series, p. 141), shows some features distinctly different from all other members of the group. Its aldehyde character and consequent ease of oxidation is one distinguishing feature, and its dehydration to give carbon monoxide is another $\text{HCOOH} \rightarrow \text{H}_2\text{O} + \text{CO}$. This dehydration takes place rather readily with hot concentrated sulfuric acid or any other strong dehydrating agent. The members of the series other than formic acid resemble each other more closely.

The most outstanding characteristic of the acids generally is the fact that they are distinct acids and have the property common to all acids of reversibly neutralizing bases with the formation of salts and water. The salts of the acids of the formic acid series are like the salts of inorganic acids in that they are crystalline substances which show a high degree of ionization in water solution. They are, of course, organic substances and as they contain carbon and hydrogen in combination, they can be burned like other organic compounds giving carbon dioxide, water, and in general the oxide of the metal which was present in the original salt. Formic acid is the strongest acid of the homologous series, acetic is the next in strength, and the strength in general decreases as the number of carbon atoms increases, though there is considerable variation. The sodium salts of these acids all give an alkaline reaction in water solution, due to hydrolysis. The salts of the higher acids, because the acids are weaker, hydrolyze more completely than the salts of the lower acids.

There is an interesting and convincing explanation on the basis of electronic structures why acids vary in strength while salts are as a rule "strong" regardless of the weakness of the acid from which they may be derived. Note the contrast between the hypothetical structure of undissociated sodium formate and that of undissociated formic acid.

Undissociated formic
acidUndissociated sodium
formate (hypothetical)

In the undissociated acid the outer shell of every atom is filled with its quota of electrons—two in the case of hydrogen and eight in the case of the other atoms. This represents a stable structure. In the undissociated sodium formate structure all the shells are filled *except that of sodium* which has only two out of eight required to complete its octet. So far as the sodium is concerned there is no element of stability attained by remaining attached to the oxygen. As an ion, broken away from its attachment, it has one (inner) shell of eight electrons complete, and is thus stable.

The strength of an acid may be greatly modified by the presence of atoms or groups in the molecule, especially if they are near the carboxyl group. This is most strikingly illustrated in the case of the chlorine substitution products of acetic acid, as shown in the table below.

STRENGTH OF ACIDS

	Ionization Constants ¹	Per Cent Ionized in .1 N Solution
Formic000214	4.52
Acetic0000180	1.33
Propionic0000134	1.13
Butyric0000149	1.22
Valeric0000145	1.22
Isovaleric000017	1.29
Methyl ethyl acetic0000169	1.25
Trimethyl acetic0000098	.99
Caproic0000146	1.18
Isobutyl acetic000015	1.22
Diethyl acetic0000203	1.40
Dimethyl ethyl acetic00000957	.99
Acetic000018	1.33
Chloroacetic00155	11.7
Dichloroacetic	(.0514)	(50.5)
Trichloroacetic	(1.21)	(93.)

¹ According to the law of mass action, the following relationship holds in a solution of an acid:

Degree of oxidation and acidity are quite closely related. In the acids containing oxygen, there is in general a hydroxyl group attached to a non-metallic element. The acids in which the most oxygen is attached to this non-metallic element are the strongest acids. This is illustrated by the following table which gives various acids arranged in the order of the amount of oxygen which is attached to the atom holding the hydroxyl group. The strengths of the different acids are in the same order; those at the right in the table with higher oxygen content are stronger acids.

$\text{H}-\text{O}-\text{N}=\text{O}$		$\text{H}-\text{O}-\text{NO}_2$	
Nitrous acid		Nitric acid	
$\begin{array}{c} \text{H}-\text{O} \\ \diagdown \\ \text{S} \text{O} \\ \diagup \\ \text{H}-\text{O} \end{array}$		$\begin{array}{c} \text{H}-\text{O} \\ \diagdown \\ \text{S} \text{O}_2 \\ \diagup \\ \text{H}-\text{O} \end{array}$	
Sulfurous acid		Sulfuric acid	
$\begin{array}{c} \text{H}-\text{O} \\ \diagdown \\ \text{H}-\text{O}-\text{P} \\ \diagup \\ \text{H}-\text{O} \end{array}$		$\begin{array}{c} \text{H}-\text{O} \\ \diagdown \\ \text{H}-\text{O}-\text{P} \text{O} \\ \diagup \\ \text{H}-\text{O} \end{array}$	
Phosphorous acid		Phosphoric acid	
$\text{H}-\text{O}-\text{Cl}$	$\text{H}-\text{O}-\text{ClO}$	$\text{H}-\text{O}-\text{ClO}_2$	$\text{H}-\text{O}-\text{ClO}_3$
Hypochlorous acid	Chlorous acid	Chloric acid	Perchloric acid

Many other examples may be given which show the same relation-

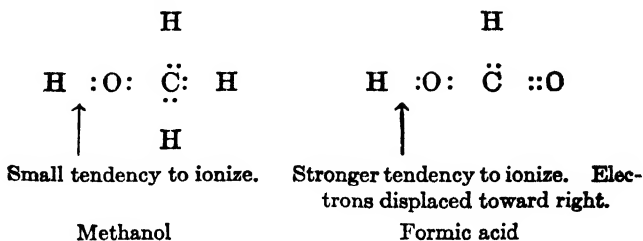
$$\frac{(\text{Conc. H}^+) (\text{Conc. Anion})}{(\text{Conc. Undissociated Acid})} = K$$

K is the ionization constant of the acid and is a measure of its strength. It is not, however, a *direct* measure and it is therefore misleading to say that formic acid is about twelve times as strong as acetic acid. It is in fact something over three times as strong in a tenth normal solution as indicated by the figures in the second column. In the case of the relatively strong acids the values (placed in parentheses) are meaningful only in a very rough way. Data for many acids, bases, and other compounds are given in Scudder, "Electrical Conductivity and Ionization Constants of Organic Compounds," D. Van Nostrand Company.

ship. A similar situation exists in the case of the organic compounds. A hydroxyl group attached to a carbon atom has a slight tendency to give rise to hydrogen ions. The more oxygen that is attached to this carbon atom, the greater is the tendency for the substance to ionize as an acid.

The very great difference in acid properties between methyl alcohol and formic acid is due to the substitution of an oxygen atom for two hydrogen atoms. The intermediate step represented by the hydrated form of formaldehyde should be intermediate in acid properties. The case is complicated by the fact that the hydrated formaldehyde is unstable and cannot be obtained in the free state. In a similar manner carbonic acid would be expected to be stronger than formic acid, since it contains more oxygen. Carbonic acid is, however, unstable and hence it is impossible to make a solution of it which has a high concentration of hydrogen ions. Its behavior as a weak acid is due probably more to its instability than to its lack of tendency to ionize. When carbon dioxide is dissolved in water presumably only a part of it combines with the water to form carbonic acid, and the carbonic acid actually present is probably rather highly ionized.

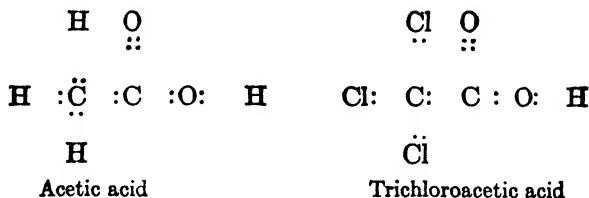
In terms of the Lewis² theory of atomic and molecular structures already alluded to, the effect of oxygen in combination on the strength of acidity is made entirely reasonable. Oxygen, like halogen, when combined with carbon has a tendency to pull the bonding pair of electrons away from carbon nucleus. This "pull of the electrons" causes a displacement throughout the whole molecule toward the oxygen atom.



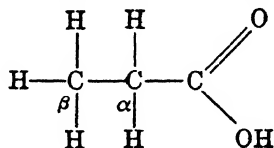
² G. N. Lewis (1875-1946) was Dean of the College of Chemistry at the University of California where he did important work both in atomic structure and chemical thermodynamics.

To avoid confusion only the electrons which are members of "bonding pairs" are represented in the figures above. It will be recalled that when a hydrogen nucleus (represented in these formulas by the symbol H) breaks away without an electron it becomes a hydrogen ion. This will take place to a much greater extent in the case of formic acid in which the bonding pair of electrons between hydrogen and oxygen is drawn closer to the oxygen. The same explanation applies to the inorganic acids cited above.

The effect of the substitution of chlorine for hydrogen in acetic acid is similar. The chlorine nucleus pulls electrons toward it and thus causes a shift or displacement of electrons in that direction. This is shown in a diagrammatic way in the figures below. Such pictures should not, of course, be interpreted literally (p. 13).



It can readily be seen that one or two substituted chlorine atoms in the acetic acid molecules would have less effect than three, and that if other strongly non-metallic elements like bromine, iodine, or oxygen are substituted instead of chlorine the acids formed, like the chloroacetic acids, would be stronger than acetic acid. If we are dealing with *propionic acid*, for example,



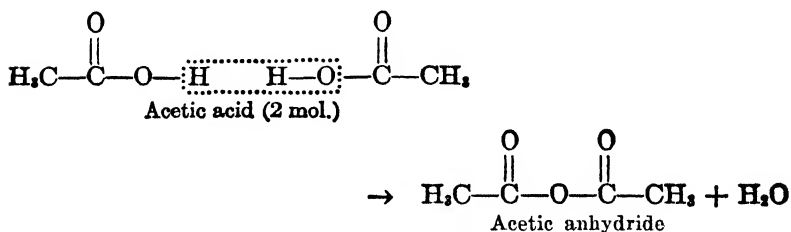
Propionic acid

we find that a substitution of chlorine (or other similar element) on either the α or β carbon atoms causes an increase in acid

The driving force for the process of ionization of an acid may be that the hydroxyl group is attached to an unsaturated atom and the separation of a proton from this structure gives a stable resonating ion.

Closely related to this problem is the fact that carboxylic acids appear to have very little tendency to enolize as compared with typical carbonyl compounds. This is shown for example by the fact that when acetic acid is dissolved in "heavy water" D_2O , interchange of D for H takes place immediately for the one "acid" hydrogen, but not for the other three, except after a long time. In contrast to this, simple aldehydes and ketones exchange all of their hydrogen for deuterium relatively rapidly. This failure to enolize appreciably may be ascribed to the presence of an ionizable group attached to the carbonyl, which seriously modifies the structure and its tendency to enolize. It may also be ascribed to existence of resonance and the absence of a typical carbonyl group in the structure of carboxylic acids.

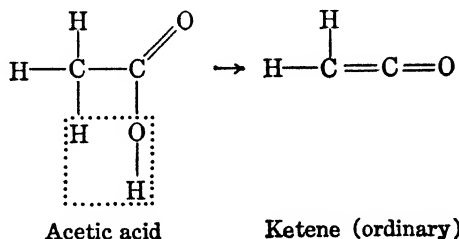
Dehydration. The decomposition of formic acid by dehydration has already been mentioned. If acetic acid is strongly dehydrated there is formed a volatile liquid with the molecular formula $C_4H_6O_3$, which is no longer an acid but by warming with water is converted into the original acetic acid. The only formula which explains this behavior is pictured below.



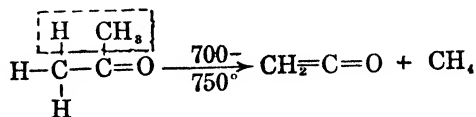
Since the dehydration product is no longer itself an acid we *might* speak of the acid as having been "neutralized" in the reaction, but this term is reserved to cases in which an acid is neutralized by a base with the formation of a salt. True neutralization reactions take place very rapidly and the salts, which are formed, are good conductors of electricity. The reaction above, however, takes place very slowly, and the product does not ionize

and hence is unlike a salt. The reaction like that between an alcohol and an acid probably takes place between molecules. In this case the product formed is a typical acid anhydride. If mixtures of more than one acid be strongly dehydrated, *mixed acid anhydrides* in small amount may be formed, though neither the mixed acid anhydrides nor the simple anhydrides are easily prepared by simple dehydration. The more useful methods of preparation of acid anhydrides will be discussed in a following chapter.

Ketenes. In acetic acid we have a hydrogen atom and a hydroxyl group attached to adjoining carbon atoms and it should be possible (p. 79) as in ethyl alcohol to remove the elements of water. This can be accomplished only with great difficulty in this case.



The product formed contains an alkene double bond, and also resembles a ketone in structure and is called a *ketene*. Ketene is readily prepared both in the laboratory and industrially by the pyrolysis of acetone.



Ketene is very reactive, takes up water with the formation of acetic acid, and may be regarded as another anhydride of acetic acid, though the term anhydride is not generally applied to it. In an analogous way ketenes are also able to add on alcohols, ammonia, and other reagents directly and undergo polymerization as might be expected from their high degree of unsaturation. Ketene is an important acetylating agent, that is, an agent for introducing acetyl (CH_3CO) groups.

Salts, Dry Distillation. The general properties of the salts of the acids of the formic acid series have already been mentioned but their decomposition at high temperature needs to be discussed because of the importance of the reactions from both the laboratory and technical standpoints.

Most organic compounds are decomposed when subjected to a high temperature. In general the simpler compounds withstand high temperatures more readily. The thermal decomposition of higher hydrocarbons (cracking) has already been mentioned. It is very natural that the thermal decomposition of salts should have claimed the attention of the early organic chemists because salts are non-volatile and can readily be subjected to high temperature. If one wishes to study the thermal decomposition (pyrolysis) of a volatile compound the experimental details are much more exacting.

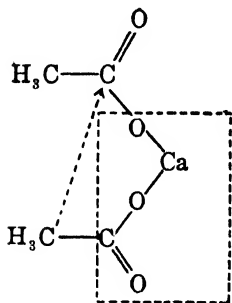
High-temperature reactions are likely to involve deep seated changes within molecules and one is not able to predict their courses from a study of reactions taking place in solution or at comparatively low temperature. When we realize that reaction rates usually at least double for each 10° rise in temperature, it becomes apparent that at 400° reactions should take place 2^{20} or over one million times as fast as at 200° . Reactions obviously become apparent at high temperature which are entirely unknown at lower temperatures. Carbon atoms break apart, free radicals are formed (p. 48) and the entire picture is quite different from anything existing in a reaction mixture at a moderate temperature.

Very often the products formed by thermal decomposition of organic compounds are varied and numerous. We shall have occasion to refer only to cases in which decomposition takes place in a relatively simple manner.³

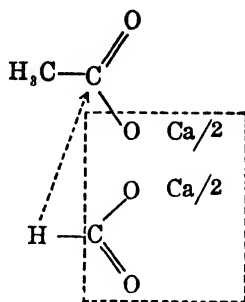
Pyrolysis of pure calcium salts of fatty acids or of mixtures of calcium salts, yields calcium carbonate as one product, and an aldehyde, ketone, or a mixture of the two, as the other products. When calcium formate is one of the salts heated, an aldehyde is one of the products formed. Typical cases are indicated below.

³ See Hurd "Pyrolysis of Carbon Compounds," Chem. Cat. Co. 1929.

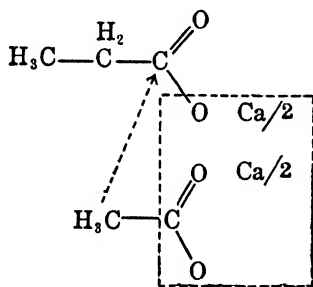
Other similar salts such as those of barium act in the same general fashion but calcium salts are more often used.



1.
Calcium acetate



2.
Calcium acetate + Calcium formate



3.
Calcium propionate + Calcium acetate

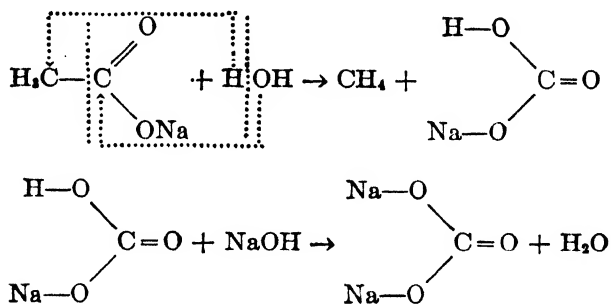
(Ca/2 is used to denote an equivalent of calcium which is present in an equivalent of the salt. By making this abbreviation it becomes unnecessary to indicate two parts of the molecule which are exactly alike.)

In reactions of the kind represented in (2) and (3) in which two different salts are heated together there is nothing to prevent two molecules of like kind from reacting with each other. Thus by heating calcium acetate and calcium formate together, three products in varying quantities will result, namely, acetaldehyde, formaldehyde, and acetone. Under experimental conditions, very large numbers of molecules are present together and some of the salt molecules can decompose independently even when

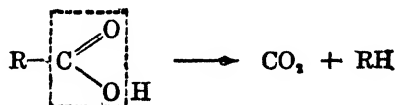
other salts are present. Therefore when two different salts must be heated together to form the desired compound, the results are likely to be unsatisfactory.

Heating of calcium formate, or other formates, alone, does not produce a good yield of formaldehyde. In cases other than those mentioned as giving unsatisfactory results, the reactions in general may be useful though they do not constitute "elegant" methods of synthesis. Heating calcium acetate (derived from wood distillation) constituted the commercial method for the production of acetone for many years.

Hydrocarbons from Salts. When sodium acetate is heated with sodium hydroxide, methane and sodium carbonate are formed. The reaction may be pictured as a hydrolysis, followed by a neutralization. By similar reactions, higher hydrocarbons can be prepared.

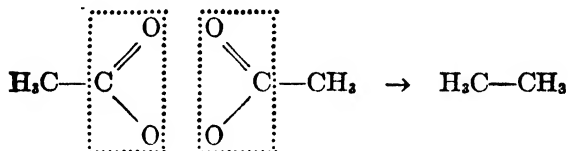


Such a hydrolysis should be expected only at high temperature. Only a trace of water would be necessary as it would be regenerated by the neutralization. Hydrolysis is probably not always a necessary accompaniment of reactions of this type. Acids which are relatively non-volatile often yield carbon dioxide when heated.



The ease with which such a reaction takes place is determined by the character of the neighboring groups in the acid molecule.

Hydrocarbons of the methane series are produced also by electrolysis of salts of the fatty acids. Sodium acetate, for example, ionizes into sodium and acetate ions which on electrolysis migrate to the respective electrodes. When the acetate ion reaches the positive electrode, according to a common conception, it gives up its negative charge. A negative ion after it is discharged often reacts with the water to liberate oxygen. Discharged chlorine ions may act in this way: $2\text{Cl} + \text{H}_2\text{O} \rightarrow 2\text{HCl} + \text{O}$. The discharged acetate ions, instead of reacting in this manner, decompose to give carbon dioxide and two methyl groups which join to form ethane. Ions of other acids in the series behave in an analogous fashion.



Higher Acids. When fats or oils (such as olive oil, etc.) are treated with superheated steam they are broken down or hydrolyzed, and part of the material formed consists of a mixture of acids of the formic acid series. These acids resemble in consistency the original fats from which they are derived, that is, they are greasy and nearly insoluble in water. Because of their origin they were called *fatty acids*, and later the name was extended so that the term is now applied to any acid of the formic acid series, whether or not it is in any way connected with fats. "*Aliphatic*" is from a Greek word meaning "fat," and is applied as a general term to all compounds which are derivatives of the methane hydrocarbons, including unsaturated compounds.

The acids which are most commonly obtained from fats are called *palmitic acid* (named from palm oil), *stearic* (stē-ār'ik) *acid* (from a Greek word meaning tallow) and *oleic* (ō-lē'ik) *acid* (named because of its source—oil; particularly olive oil). The student must guard against the misconception that the fatty acids constitute the fats. Fats are esters. Palmitic and stearic acids are the sixteenth and eighteenth normal members, respectively, of the formic acid or fatty acid series. There are, of

course, a very large number of possible isomers in the cases of the higher acids, but the acids which are abundant in nature are normal (straight chain) acids. Other acids procurable from fats are like palmitic and stearic in that they always have even numbers of carbon atoms. This practically invariable rule suggests the idea that in the building up of fats by plants or animals the building up of the acids takes place with the addition of even numbers of carbon atoms at a time.

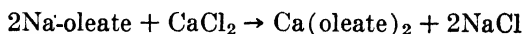
Oleic acid is related to stearic acid closely, in that by reducing it stearic acid is produced. Oleic acid is an unsaturated acid, that is, it has in its structure two carbon atoms which are doubly bonded. One mole of oleic acid is able to take up one mole (2 atoms) of iodine or of hydrogen. Oleic acid is a liquid at ordinary temperatures while stearic acid is solid.

Soaps. When, as is often the case, a fat is treated with an alkali instead of superheated steam, the same reaction occurs except that the alkali salts of these same fatty acids are formed. These salts are known as soaps, and the better grade of soaps, as they are sold, consist largely of mixtures of the sodium salts of higher acids. Castile soap made from olive oil is largely sodium oleate. Most soaps contain more or less glycerin, and many contain rosin which has been treated with alkali. Potassium salts of these same acids can be used in the same way, but are soft soaps, and are less easily handled as well as more expensive because of the potassium they contain.

Soaps behave in every way like salts of the lower acids, except that when dissolved in water a soap does not break down into molecules, but remains as aggregates or clusters of molecules. If one should attempt to determine the molecular weight of sodium oleate by the freezing point or the boiling point method, using water as a solvent, the result would show that the soap has a negligible effect on the freezing point or the boiling point, and hence the particles are few in number and very large. However, the results obtained when alcohol is used as a solvent (boiling point method) show that the aggregates are lacking; the soaps exist in alcohol solution molecularly dispersed.

Even in water solution soap often yields results like those of a molecular solution. Like salts of the lower acids of the series

the soaps hydrolyze in solution and thus produce a slight alkaline reaction. Similarly, if the solution of some other salt is added to a soap solution, a precipitation reaction involving a simple interchange of ions may take place. If, for instance, a soluble calcium salt such as calcium chloride is added to a soap solution, the following reaction takes place:



Calcium oleate is practically insoluble in water and hence the reaction goes practically to completion. Only the salts of the alkali metals are soluble in water so that, by the addition of a solution of a salt other than salts of the alkali metals, insoluble soaps (salts) are formed. Thus we may have calcium soaps, magnesium soaps, lead soaps, copper soaps, etc., all of which are insoluble.

Hard water contains soluble salts of calcium or magnesium, and as soon as a soluble soap is added to a hard water, the soluble soap is converted to an insoluble calcium or magnesium soap which does not function as a cleansing agent. Salts of other metals if present would produce the same result, but these are the ones which are so often present in natural waters.

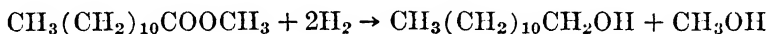
Cleansing Action of Soaps. Of course only those soaps which are soluble in water are useful as cleansing agents. The full discussion of how soaps cleanse does not belong here, but the fact that fats and greases may be emulsified or in a sense brought into water solution by soap may be discussed briefly with profit. There is evidence that in a film of soap on the horizontal surface of pure water, the sodium parts of the molecules, including the carboxyl group to which they are attached, are in the water while the other ends of the molecules (hydrocarbon part) are directed upward and are out of the water. In other words, one end of the soap molecule is soluble in water while the other end is insoluble. A fat or grease is insoluble in pure water but is soluble in the hydrocarbon part of the soap molecule. The soap then acts as a "go-between" or connecting link, as one part of the soap molecule dissolves the fat while the other part dissolves in the water. This serves to give us a clue as to how and why the soap acts. The aggregates of soap molecules in water have the

FATTY ACIDS

Acid	Formula	Density	Melting Point	Boiling Point	Solubility in 100 ml.		
					Water	Alc. (20°)	Ether (20°)
Formic (methanoic)	HCOOH	1.218 (20°)	8.6	100.8	inf.	inf.	inf.
Acetic (ethanoic)	CH ₃ COOH	1.051 (20°)	16.7	118.1	inf.	inf.	inf.
Propionic (propanoic)	CH ₃ CH ₂ COOH	.987 (20°)	-22	140.7	inf.	inf.	inf.
Butyric (n) (butanoic)	CH ₃ (CH ₂) ₂ COOH	.960 (19°)	-7.9	163.5	inf.	inf.	inf.
Butyric (iso)	(CH ₃) ₂ CHCOOH	.949 (20°)	-47	155	20 (20°)	inf.	inf.
Valeric (pentanoic)	CH ₃ (CH ₂) ₃ COOH	.942 (20°)	-58.5	186	3.7 (16°)	inf.	inf.
Valeric (iso)	(CH ₃) ₂ CHCH ₂ COOH	.936 (22°)	-51	176	4.2 (20°)	inf.	inf.
Methylethylacetic	CH ₃ CH(C ₂ H ₅)COOH	.938 (20°)	(-37.6)	174	sl.s	inf.	inf.
(2-methylbutanoic)	CH ₃ CH(C ₂ H ₅)COOH		-90				
Trimethylacetic	(CH ₃) ₃ CCOOH	.905 (5°)	35.5	163.7	2.2	v.s.	v.s.
(2,2-dimethylpropanoic)	CH ₃ (CH ₂) ₂ COOH	.925 (25°)	-3.2	205.8	1.2 (60°)	inf.	inf.
Caproic (hexanoic)	CH ₃ (CH ₂) ₄ COOH	.910 (20°)	16.5	239.7	0.1 (60°)	inf.	inf.
Caprylic (octanoic)	CH ₃ (CH ₂) ₆ COOH						
Capric (decanoic)	CH ₃ (CH ₂) ₈ COOH						
Lauric (dodecanoic)	CH ₃ (CH ₂) ₁₀ COOH	.886 (40°)	31.4	270.0	0.03 (60°)	inf.	v.s.
Myristic (tetradecanoic)	CH ₃ (CH ₂) ₁₂ COOH	.874 (45°)	43.9	130.5 (1 mm)	i.	72.2	v.s.
Palmitic (hexadecanoic)	CH ₃ (CH ₂) ₁₄ COOH	.853 (70°)	54.2	149.2 (1 mm)	i.	15.1	s.
Stearic (octadecanoic)	CH ₃ (CH ₂) ₁₆ COOH	.841 (80°)	62.8	167.4 (1 mm)	i.	3.9	s.
Arachidic	CH ₃ (CH ₂) ₁₈ COOH	.839 (80°)	69.6	183.6 (1 mm)	i.	0.9	sl.s.
Melissic	C ₃₀ H ₆₀ O ₂	77	i.	0.5	sl.s.
	C ₃₀ H ₅₈ O ₂	90	i.	sl.s.	sl.s.

sodium ends of the molecules pointing outward and in contact with the water while the hydrocarbon parts of the molecules are directed inward and in contact with each other. The fat or grease on being rubbed with the soap becomes incorporated in the inside of these soap aggregates which expand and subdivide as long as there is soap enough to form the outer water-soluble "jacket."

Newer Detergents. The production of lauryl alcohol by the hydrogenolysis of lauric acid esters has been mentioned (p. 84). Coconut oil yields about 45 per cent lauric acid which is converted into its methyl ester and subjected to reduction and splitting by the catalytic action of hydrogen.



This alcohol is converted to the mono ester of sulfuric acid $\text{CH}_3(\text{CH}_2)_{10}\text{CH}_2\text{OSO}_2\text{OH}$, which in the form of the sodium salt has a structure typical of some of the newer detergents. They have the advantage that since they are salts of strong acids they are neutral in reaction (for example, they will not cause one's eyes to smart) and do not form insoluble soaps in hard water. Dreet, Irium and Gardinol are trade names under which such detergents are sold. There are more than 200 synthetic detergents available in the United States.

Ethanolamine soaps are mentioned in a later section (p. 235).

PROBLEMS

1. By dry distillation of 50 g. of calcium acetate there were produced 12 g. of acetone. What percentage is this of the theoretically possible yield?
2. Suppose 10 ml. of exactly .2 N acetic acid solution is added to 10 ml. of exactly .2 N sodium hydroxide solution. Would the resulting mixture give an acidic, basic or neutral reaction to a sensitive neutral indicator? Why?
3. How many cc. of propane gas (standard conditions) could theoretically be obtained from 5.5 grams of sodium butyrate?
4. If a sample of water gas contained 37 per cent carbon monoxide, how much sodium formate could theoretically be obtained from 22,400 liters of the gas, measured at standard conditions?
5. What products would you expect to be formed by the electrolysis of sodium formate?

6. What salt should you expect to be formed by the interaction of sodium ethylate and carbon monoxide?

7. What salt mixture might be expected to yield methane by electrolysis?

8. Explain why it is that although acetic acid is only about one per cent ionized in .1 N solution, a mole is capable of neutralizing as much alkali as a mole of chloroacetic acid which is about 12 per cent ionized under the same conditions.

9. How much soap (sodium oleate containing, say, 50 per cent water) would be used up by a liter of saturated calcium sulfate solution (.179 g. per 100 cc. of water)?

10. One gram of a salt of an acid of the fatty series yielded almost exactly 1 gram of silver iodine when treated with NaI. What salt was it?

11. A copper soap (cupric salt of monobasic acid) contains 19.92 per cent copper; what is the molecular weight of the acid?

12. Write the formulas of the products formed by the addition of (a) methyl alcohol, (b) ammonia, to ketene. What would be the formula for methyl ketene?

13. Sodium acetate is used extensively especially in the dyestuff industry to reduce the H^+ concentration of acid solutions. Indicate how this operates.

14. When acetic acid is dissolved in deuterium oxide, one hydrogen atom only is exchanged quickly. What does this indicate as to the enolization of acetic acid?

15. Acids are reduced with difficulty. What reason is there for thinking that their tendency to ionize is responsible for this fact?

16. What is the effect on the ionization constants of acids, of having three alkyl groups attached to the α carbon atom? Do alkyl groups have a similar effect in alcohols?

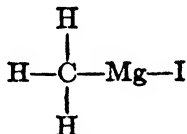
17. In terms of enolization explain why trimethyl acetic acid does not yield a bromine derivative readily whereas dimethyl acetic acid readily yields $(CH_3)_2CBr - COOH$.

CHAPTER IX

GRIGNARD REAGENTS

Before discussing the derivatives of the acids (Chapter X) we shall consider a group of very useful reagents, which, though they may not seem to fit logically into our discussion at this point, are very useful for preparing acids and other compounds with which we have already dealt. For the first time we are prepared to consider these reagents without bringing unfamiliar compounds into the discussion.

When an alkyl halide,¹ especially in anhydrous ether solution, is heated gently with metallic magnesium, the metal goes into solution and a product is formed which is usually represented as follows (when methyl iodide is the alkyl halide used).



Methyl magnesium iodide

Although various other metal derivatives are known in which zinc, mercury, lead and even alkali metals are attached directly to carbon, they are by no means as important as the Grignard ² reagents which contain magnesium. The particular example cited above is only one of a large number of Grignard reagents which

¹ The alkyl iodides are the most reactive, the bromides next and the chlorides least, reactive, in this as well as in other reactions. The order of expensiveness is the same as the order of reactivity, so that bromides and chlorides are often used for economy in spite of their lower reactivity. In the case of the methyl halides, both the bromide and chloride are gases and thus difficult to handle. Ethyl chloride is also a gas and is not often used on this account. See table on page 39.

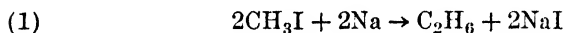
² Victor Grignard (1871-1935) was professor of chemistry at Lyon, France. The reagents were discovered in 1900. Grignard was at that time studying under Barbier who deserves part of the credit for the discovery.

can be prepared from the various alkyl halides. Their extreme usefulness in the synthesis of various organic compounds will be apparent from our further discussion.

Ionization. A survey of the various types of compounds containing strongly metallic atoms reveals the fact that these elements exist most often as potential positive ions. When sodium or calcium are attached even to hydrogen (a metal-like element) they lose electrons to it forming positive metal ions and *negative* hydrogen ions. The Grignard reagents are no exception in this regard and investigations of the electrolysis of these substances in ether solution indicate that the magnesium-carbon bond is one which is capable of ionization to yield *negative* alkyl ions.

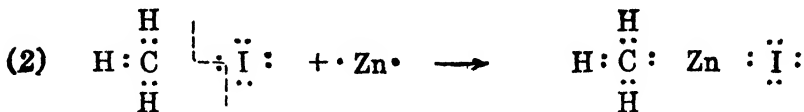
A complete discussion of the complex valence phenomena that the Grignard reagents exhibit involves certain conceptions which we are not yet ready to present, but certain elementary points may be clarified at this time.

When a metal reacts with an alkyl halide there are three possibilities which are of importance. In case the metal is very active (and with one outer shell electron) the reaction is of the Wurtz type.

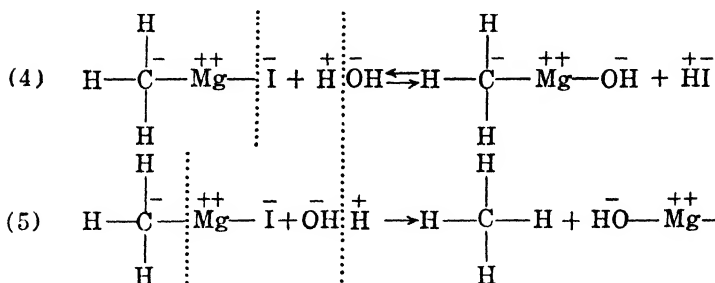


The strong tendency of the sodium to lose its electron coupled with the fact that in the methyl iodide the electron-attracting iodine atom must share one pair of electrons and cannot have complete possession of them, allows the transfer to take place so that the iodine obtains complete possession and thus becomes an iodide ion. Simultaneously neutral methyl groups are freed and their lone electrons pair off to form the C-C bond in ethane.

When a metal is bivalent another possibility results, the metal atom may lose one electron to the halogen atom which thereby becomes an ion (or a potential ion) and another to the neutral methyl group which lacks one electron of having an octet.

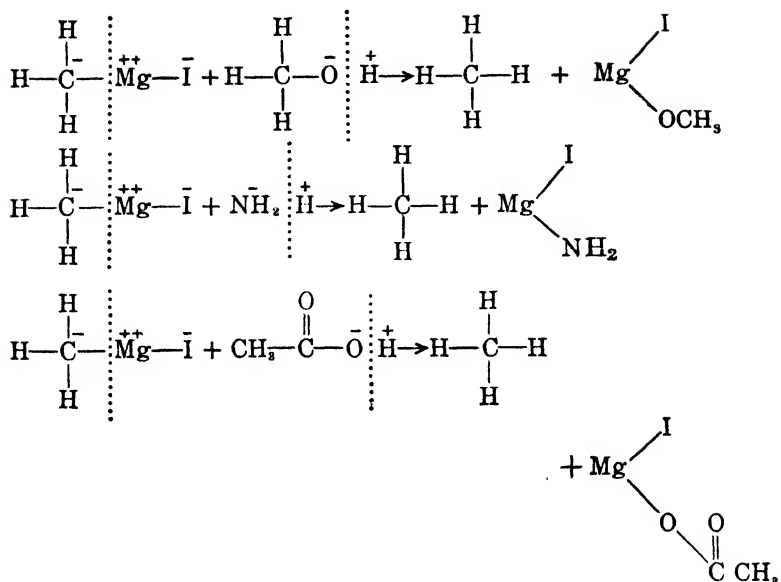


Still another possibility is that each of two metal atoms may lose electrons to the halogen and to the carbon of the methyl group. In this case the reaction may be pictured thus:



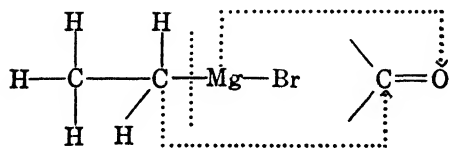
Reaction (4) would not take place appreciably toward the right because a strong acid and base are formed, which would cause the reaction to reverse. In reaction (5), however, methane is formed which is a volatile gas and not ionized, hence this reaction should go to completion. The reaction goes very vigorously in exactly this way to form methane. In case the Grignard reagent is ethyl magnesium bromide, $\text{C}_2\text{H}_5\text{MgBr}$, ethane is produced on treatment with water. These reactions constitute a method for small scale laboratory preparation of methane, ethane, propane, and other paraffin hydrocarbons.

Reactions with Alcohols, Ammonia, and Acids. Since alcohols have weakly acidic properties, they would be expected to react with Grignard reagents in a way similar to water. The methoxy group, OCH_3 , of methyl alcohol should play the rôle of the hydroxyl group of water. Similarly, since anhydrous ammonia has weak acidic properties a similar reaction would be expected with this reagent. In this case the amino group, NH_2 , should play the part which the hydroxyl group plays in the reaction with water. Acetic acid or other acids might be expected to react in a similar manner, since they furnish hydrogen ions to a much greater extent than water, alcohols, or ammonia. The Grignard reagents react just as would be expected in these cases, according to the following equations. Water and the distinct acids are more reactive than alcohols or ammonia. It is interesting, however, that even alcohols and ammonia are strong enough "acids" to liberate methane which shows no evidence of ionization.



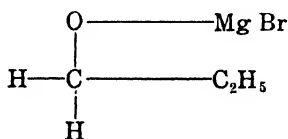
By these reactions hydrocarbons are produced, but since hydrocarbons of the methane series are of little value in synthetic work, these reactions are not of great practical importance. One of the simplest Grignard reagents has been used as an illustration above; more complicated ones act in a similar manner.

Reactions with Substances Containing the Carbonyl Group. Grignard reagents form addition products with substances which have the carbonyl group in their structure. (With acids the reaction is as pictured above.) The Grignard reagents break in these addition reactions at the same place as they do in

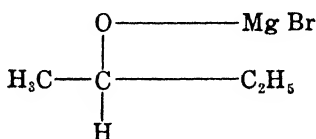


reacting with water, and the substances having the carbonyl group add on the Grignard reagents in the same manner as they add on sodium bisulfite; the oxygen is negative and takes up the

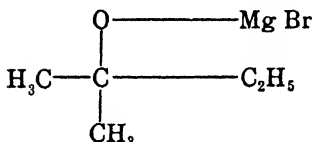
positive group of the Grignard reagent while the carbon takes up the negative group. Whether the substance containing the carbonyl group is an aldehyde, ketone, ester of a carboxylic acid, or carbon dioxide, this addition reaction takes place in the same way, and these constitute the most important reactions of the Grignard reagents. Below are indicated the additions in a number of typical cases.



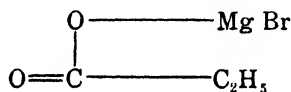
Formaldehyde +
Ethyl magnesium bromide



Acetaldehyde +
Ethyl magnesium bromide



Acetone +
Ethyl magnesium bromide



Carbon dioxide +
Ethyl magnesium bromide

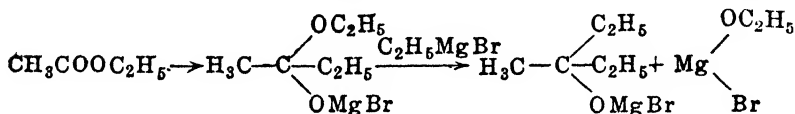
Each of the products is formulated as a mixed magnesium salt of hydrobromic acid and another "acid." The other "acids" in the first three cases are a primary, secondary and tertiary alcohol, respectively; in the fourth case it is propionic acid. In those cases where the magnesium is attached to the oxygen of an alcoholic hydroxyl group it is easily removed by hydrolysis just as sodium is eliminated from sodium ethylate. The mixed salt of hydrobromic and propionic acids (which is equivalent as in the other cases to a mixture of the two salts) is not decomposed by water alone, and the acids must be freed by heating with a non-volatile acid after the general method of preparing an acid from its salt.

These are typical examples, and it is evident that a great variety of alcohols of the three types, and of acids, can be prepared by use of Grignard reagents utilizing the appropriate alkyl halides and carbonyl compounds. The alcohols obtained in this

way may likewise by oxidation be converted into a variety of aldehydes and ketones and acids.

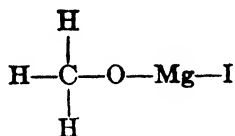
Theoretically it should be possible to prepare practically any primary, secondary or tertiary alcohol, but experimentally it is found that when the compounds involved have complex branched chains interference results which may make it impossible to bring about the usual Grignard syntheses. When the carbonyl group is shielded by complex groups which tend to surround it, addition does not take place, but side reactions which normally are not significant become predominant. Among these are direct reduction of the aldehyde or ketone, and various condensations.

With esters of carboxylic acids and acid chlorides (p. 155) the simple addition to the carbonyl group is accompanied by a substitution of an alkyl group from a second molecule of the Grignard reagent, for the alkoxy group or the chlorine, of the original carbonyl compound. This constitutes another method for preparing a tertiary alcohol.



The Grignard reagents react similarly with compounds containing the $=\text{C}=\text{S}$ and $-\text{C}\equiv\text{N}$ groups and form addition products which can be hydrolyzed. These sulfur and nitrogen compounds are to be studied later. Grignard reagents also react with a few other compounds such as ethylene oxide (p. 234); these reactions will be mentioned in later discussions.

Oxidation. Grignard reagents absorb dry oxygen gas. In the case of methyl magnesium iodide a substance with the formula



is formed. This can be hydrolyzed to give methanol. The method of preparation, however, is not important, since methyl iodide from which the above Grignard reagent is made is itself prepared from methanol.

Reactions with Inorganic Halides. The Grignard reagents react by double decomposition with halides of various elements.

For example, with silicon tetrachloride, magnesium ethyl bromide may form any of the following substances depending on the proportion of the Grignard reagent used.



The Grignard reagents are so varied and their reactions are so numerous that we are obliged to limit our discussion to the more important cases. These reagents are not limited to those which have one halogen atom in the molecule, and several substances react with the typical reagents readily, which have not been discussed in this connection. One of the advantages of the Grignard reagents is the fact that for use in the laboratory they need not be purified before use. They usually are prepared immediately before they are used as a synthetic reagent and they often react in a straightforward manner.

PROBLEMS

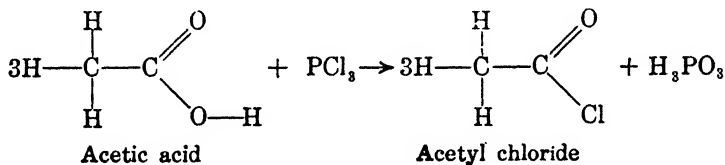
1. Indicate how propyl magnesium iodide reacts with (1) water, (2) ammonia, (3) acetic acid, (4) acetone.
 2. How could both ethyl iodide and propyl iodide each be made to yield propanol using Grignard reactions?
 3. What alcohol could be prepared making use of the reaction of gaseous formaldehyde on butyl magnesium chloride? How would "formalin" react with a Grignard reagent?
 4. Outline how each of the four butyl alcohols can be prepared making use of Grignard reagents with no more than three carbon atoms per molecule.
 5. How many ketones are possible having five carbon atoms? Show how each of these could be prepared making use of Grignard reactions.
 6. What product would you expect to result from the reaction of methyl sodium and carbon dioxide?
 7. How would diethyl zinc, $\text{Zn}(\text{C}_2\text{H}_5)_2$, react with (a) water, (b) alcohol?
 8. Write equations for the reactions involved in the formation of tetraethyl silicon.
-
9. How can the compound with the structure $\text{CH}_3\text{CH}_2\text{C}(\text{COOH})(\text{CH}_3)_2$ be prepared (several steps) using the following reagents (1) magnesium, (2) water, (3) HBr , (4) CO_2 , (5) ethyl alcohol, (6) acetone?

CHAPTER X

ACYL HALIDES, ANHYDRIDES OF FATTY ACIDS, ESTERS AND AMIDES

Acyl Halides

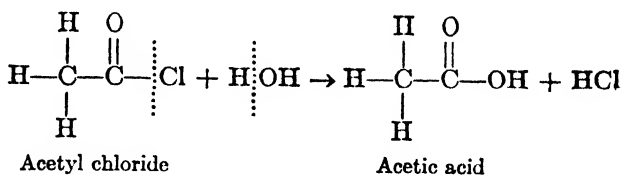
When pure acetaldehyde is treated with chlorine gas a substitution product is formed which evidently has the structure indicated in the equation below. That the liquid formed actually has this structure is evidenced not only by its formation from acetaldehyde but also by the fact that it can be made by the action of phosphorus trichloride or thionyl chloride, SOCl_2 , on acetic acid. In these reactions chlorine is substituted for the hydroxyl group.



Acetyl chloride (CH_3CO is the acetyl group) is, in fact, prepared most often by one of the latter methods; the reaction between acetaldehyde and chlorine is not used because the reagents are not conveniently handled and the reaction does not stop readily at the desired point. *Acetyl* (äs'ê-tîl) *bromide* and *acetyl iodide* are similar in general properties to acetyl chloride but much less important. Acetyl chloride is one of a series of homologous compounds. Formyl chloride (derived from formic acid) is unstable and has been isolated only at liquid air temperature, but acid chlorides of the higher acids are well known. The general term *acyl* (äs'îl) *chlorides* is applied to the homologous series. They are also called *acid chlorides*. In this discussion of acyl halides acetyl chloride will be used to illustrate the general reactions and properties of this type of compound because

acetyl chloride is not only typical but is by far the most important.

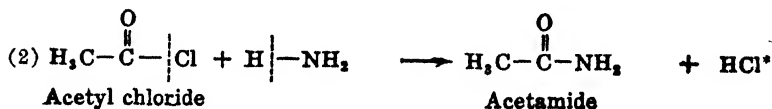
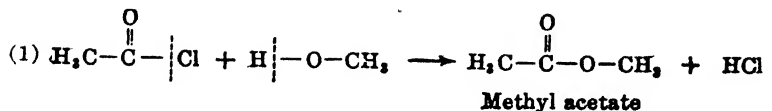
Hydrolysis. When acetyl chloride comes in contact with water, it reacts vigorously to produce hydrochloric and acetic acids according to the equation



Acetyl chloride is thus the mixed anhydride of hydrochloric and acetic acids, and in general properties such as volatility and failure to undergo ionization, it resembles other anhydrides. It is more reactive and hydrolyzes more readily than anhydrides of weaker acids. Probably this increased reactivity in the anhydrides of stronger acids is due to increased distortion of the electron shells of the atoms in the anhydrides. Such distortion might be expected as a result of the presence of oxygen and other so-called negative (electron attracting) atoms or groups.

Although acetyl chloride reacts readily with water it is formed in small amounts by the reverse of the above reaction, when glacial acetic acid and hydrogen chloride are heated together with phosphorus pentoxide.

Alcoholysis, Ammonolysis. Acetyl chloride also reacts readily with alcohols and with ammonia in a manner analogous to the reaction with water.



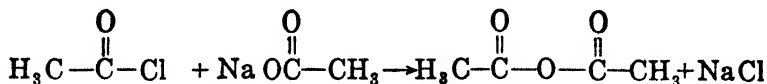
* NH_4Cl is actually formed in this and similar cases. Two equivalents of ammonia are then involved in the reaction.

The products of these reactions are an ester and an amide (ām'id) respectively, and are to be discussed shortly. It is only necessary to mix the reagents in order to have reactions go practically to completion in accordance with the above equations. Reactions similar to (I) above take place with the more complex alcohols, and the product formed in each case is the acetic acid ester of the alcohol in question. With ammonia derivatives (to be studied later) which contain the amino group ($-\text{NH}_2$) or the imino group ($>\text{NII}$), reactions similar to those with ammonia take place.

The fact that an unknown compound reacts with acetyl chloride gives indication of the nature of the compound and often the product formed by this reaction can easily be purified and identified or reconverted into the pure alcohol or ammonia derivative from which it was formed. In case of a compound which, in its structure, contains more than one alcoholic hydroxyl group or more than one amino group (NH_2), the number of hydroxyl or amino groups present may be ascertained by determination of the amount of acetyl chloride which is acted upon by a given weight of the compound in question. If a mole of a compound reacts with one mole of acetyl chloride, this indicates that there is only one hydroxyl or amino group in its structure.

If in the above hydrolysis and analogous reactions the corresponding sodium compounds are used, *e.g.*, NaOH , NaOCH_3 and NaNH_2 , the reactions are even more vigorous forming sodium chloride as one product.

Reaction with Fatty Acid Salts. Acetyl chloride as well as other acyl halides will in general react with fatty acids in a manner strictly analogous to their reactions with water, but the reactions do not usually take place readily, and sodium salts of fatty acids are used instead, as exemplified below. This con-



stitutes an important general method for the preparation of a new type of compound, the fatty acid anhydride.

Distinctive Features of Anhydride Reactions. It will be

noted that water and alcohols react more readily with acetyl chloride and acetic anhydride than does acetic acid (a much stronger acid). This fact emphasizes the point of view that none of these reactions in which anhydrides take part involve ionic interchange, and hence the futility of attempting to apply the concepts of ionic reactions. If the reactivity of the reagents were based upon their tendency to ionize then an aqueous hydrochloric acid solution should react with acetic anhydride to form acetyl chloride and acetic acid but instead the water reacts while the hydrochloric acid remains inert.

The reactions of anhydrides with various reagents are best correlated with each other when the greater reactivity of anhydrides of strong acids is thought of in contrast to the lesser reactivity of the anhydrides of weak acids. Reactions take place in the direction of the formation of products which under the conditions used are more stable. *If a reaction involves conversion of an anhydride of stronger acids into an anhydride of more weakly acidic substances the reaction is likely to take place, but the reverse is not to be expected.*

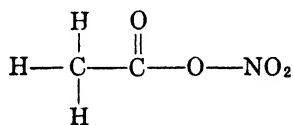
At best it is not possible to predict with accuracy exactly what type of reactions an anhydride will undergo, or exactly what direction a given reaction may take in case there are several possibilities. The above generalization is of material help, however, and applies to many cases. Any attempt on the part of the student to interpret the reactions in terms of the familiar concepts of ionic reactions will be worse than useless because most often he will be led to a conclusion in direct opposition to the facts.

ACYL HALIDES
(Mixed anhydrides of fatty and halogen acids)

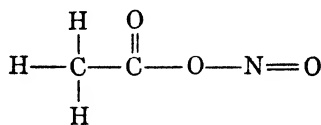
	Formula	Boiling Point
Formyl chloride	HCOCl	Unstable
Acetyl chloride	CH_3COCl	52°
Propionyl chloride	$\text{CH}_3\text{CH}_2\text{COCl}$	80°
Butyryl chloride	$\text{CH}_3\text{CH}_2\text{CH}_2\text{COCl}$	101°
Valeryl chloride	$\text{CH}_3(\text{CH}_2)_4\text{COCl}$	128°
Acetyl bromide	CH_3COBr	76.7°
Propionyl bromide	$\text{CH}_3\text{CH}_2\text{COBr}$	104°
Acetyl iodide	CH_3COI	108°
Propionyl iodide	$\text{CH}_3\text{CH}_2\text{COI}$	127°

The **reduction** of acyl chlorides to aldehydes and primary alcohols is of some importance, since it can be carried out readily. The easiest method of reducing a carboxylic acid to the corresponding aldehyde or alcohol is to first convert it into the acid chloride (or ester) which is much easier to reduce than the acid itself.

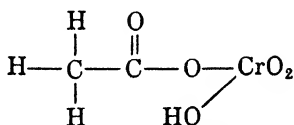
The compounds listed above are mixed anhydrides of fatty acids and halogen acids. The following are examples of mixed anhydrides of fatty acids and other inorganic acids.



Acetyl nitrate



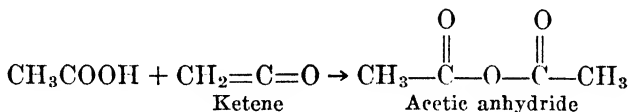
Acetyl nitrite



Acetyl chromate

Anhydrides of Fatty Acids

The preparation of acetic anhydride from acetyl chloride and sodium acetate has already been mentioned as well as the fact that it is formed in small amount when acetic acid is heated with phosphorus pentoxide. Acetic anhydride may also be made by passing ketene (p. 137) into acetic acid. This is an industrial method of preparation.



Acetic anhydride is a volatile liquid with a boiling point above that of acetic acid, and is the simplest member to be prepared of the homologous series of simple acid anhydrides of fatty acids. Formic acid anhydride like formyl chloride is unstable

and has never been isolated. Besides the simple acid anhydrides, mixed anhydrides of fatty acids are known, such as are mentioned in the table below.

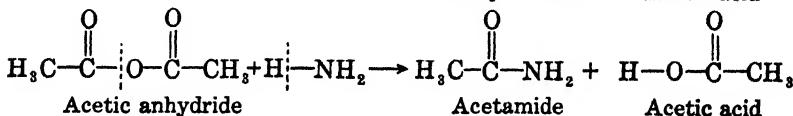
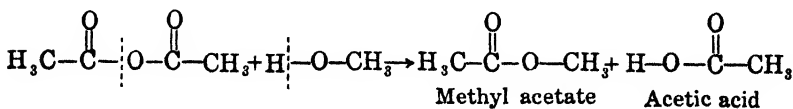
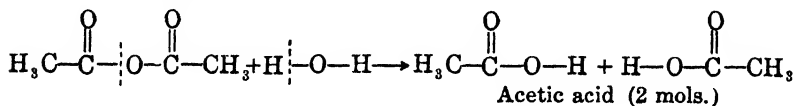
SIMPLE ANHYDRIDES OF FATTY ACIDS

Name	Formula	Density	Boiling Point	Solubility in 100 ml.		
				Water	Alcohol	Ether
Acetic anhydride...	$(\text{CH}_3\text{CO})_2\text{O}$	1.082 (20°)	140	dec.	inf.	inf.
Propionic anhydride	$(\text{CH}_3\text{CH}_2\text{CO})_2\text{O}$	1.010 (20°)	168.6	dec.	dec.	inf.
Butyric anhydride..	$(\text{CH}_3\text{CH}_2\text{CH}_2\text{CO})_2\text{O}$.995 (20°)	198	dec.	dec.	inf.
Valeric anhydride..	$(\text{C}_5\text{H}_9\text{O})_2\text{O}$.927 (27°)	215	dec. hot	—	v.s.

MIXED ANHYDRIDES OF FATTY ACIDS ¹

Name	Formula	Boiling Point
Formic acetic anhydride..	HCOOCOCH_3	105-120 decomp.
Acetic butyric anhydride..	$\text{CH}_3\text{COOCOCH}_2\text{CH}_2\text{CH}_3$	155-157
Acetic isovaleric anhydride	$\text{CH}_3\text{COOCOC}(\text{CH}_3)_3$	175-181

Hydrolysis, Alcoholysis, Ammonolysis. Acetic anhydride, like acetyl chloride, reacts with water, but the reaction is less vigorous, and part of the acetic anhydride may remain dissolved in the water unchanged for some little time. Acetic anhydride also reacts with alcohol and ammonia just as acetyl chloride does but not so rapidly.



¹ Anhydrides of this type are hard to isolate as they readily change into a mixture of simple anhydrides.

The last reaction is complicated by the fact that ammonia combines directly with acetic acid as soon as it is formed, so that two equivalents of ammonia must be present for complete reaction of the anhydride, ammonium acetate is formed instead of acetic acid as indicated. The above reactions are not restricted to acetic anhydride but are typical of anhydrides in general.

Since alcohols and most derivatives of ammonia react with acetic anhydride, it, like acetyl chloride, is used as a reagent to react with these compounds. Both acetyl chloride and acetic anhydride are spoken of as acetylating agents since they both bring about an introduction of an acetyl group. The products formed can be used in the identification or purification of the alcohols or ammonia derivatives. About 600 million pounds per year of acetic anhydride are produced and used to make acetates of which cellulose acetate (p. 375) is the most important.

Esters

The three principal methods by which esters are prepared have already been mentioned, namely, by direct reaction between acid and alcohol and by alcoholysis of acid chlorides and acid anhydrides. The first method involves only one step and hence is preferable when it can be applied. In the other cases the acid would ordinarily have to be converted first into an anhydride (simple or mixed) which in a second reaction would then be treated with the alcohol.

While the direct action between two molecules of a fatty acid to produce an acid anhydride is not practicable, due to the near irreversibility of the hydrolysis reaction, the formation of esters by the interaction of acids and alcohols is often (though not always) a very convenient laboratory procedure. The two types of anhydride formation differ in degree rather than kind. Both reactions may be carried out with a minimum of water present; the products in the two cases are volatile liquids which give no evidence of ionization. The esterification reaction, especially, is known to be slow (rather than the rapid ionic type) and like the formation of acid anhydrides cannot be interpreted successfully in terms of ionic interchange.

Esters may be regarded as mixed anhydrides of acids and alcohols just as acyl chlorides are mixed anhydrides of fatty acids and hydrochloric acid. Since both alcohols and acids are acidic in character (though alcohols are not commonly termed "acids") the esters may be regarded as belonging to a large group of *acidic anhydrides* in which acyl chlorides, fatty acid anhydrides and even ethers are included. The term *acid anhydride* should be reserved for use in connection with those substances which yield two distinct acids on hydrolysis.

Reaction Rates and Equilibrium in Esterification. When we speak of the readiness with which a reaction takes place we should, strictly speaking, specify more clearly what is meant. There are two factors which may be in mind, one is the *rate* at which the reaction takes place, the other is the *extent* to which it takes place, if allowed to come to equilibrium. The two measures are entirely different in that a reaction may proceed immeasurably slow and yet, given time enough, go practically to completion. Such is the case in the reaction $2\text{H}_2 + \text{O}_2 \rightarrow 2\text{H}_2\text{O}$ at ordinary temperature.

In the case of the hydrolysis of esters and like compounds in which reactions comparatively little energy is involved, there is some parallel (though by no means a perfect one) between the *rates* at which hydrolyses occur under comparable conditions and the *extents* to which they take place at equilibrium. This parallelism is in a certain sense fortuitous. The tendency of anhydrides of stronger acids to hydrolyze *both* more rapidly *and* more completely is shown in the data which are presented.

Comparative Hydrolysis Rates with Water Alone at 25°

	K _w
Ethyl acetate0000000092
Acetic anhydride175
Propionic acetic anhydride121
Propionic anhydride087

Comparative Alkaline Hydrolysis Rates at 25°

	K	K _a of acid involved
Ethyl formate	Too rapid to measure	.000214
Ethyl acetate	6.56	.000018
Ethyl propionate	5.94	.0000134
Ethyl hydroxyacetate	65.3	.000152
Ethyl α hydroxypropionate	63.7	.00014
Ethyl β hydroxypropionate	10.2	.00003

	K	K _a of acid involved
Comparative Acid Hydrolysis Rates at 25°		
Methyl formate145	.000214
Ethyl formate187	
Methyl acetate00680	.000018
Ethyl acetate00658	
Methyl propionate00724	.0000134
Ethyl propionate00706	
Methoxymethyl acetate (CH ₃ OC'H ₂ OOCH ₃)143	
Methoxymethyl propionate0925	

Equilibrium Constants (acid conditions)

	$\frac{K \text{ hydrolysis}}{K \text{ esterification}}$ at 100°	
Methyl formate	1.03	.000214
Ethyl formate883	
Methyl acetate224	.000018
Ethyl acetate332	
Methyl propionate214	.0000134
Ethyl propionate294	
Ethyl hydroxyacetate44	.00015
Ethyl α hydroxypropionate38	.00014

Esterification and hydrolysis reactions involve comparatively little energy and as a result the equilibrium between an alcohol, acid, ester and water does not shift very much with the temperature.

Van't Hoff's law,

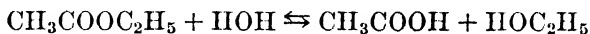
$$\frac{d \ln K}{dt} = \frac{\Delta H}{RT^2}$$

in which K is equilibrium constant of a reversible reaction, T is the absolute temperature, ΔH is the heat of reaction, R is the gas constant, shows that changes in equilibrium constants are a direct function of heat of the reaction. The *equilibrium* in the case in which ethyl acetate is concerned is actually not shifted more than about one per cent for 100° temperature change. (The time necessary for the establishment of such equilibrium decreases greatly with rise in temperature.)

Catalysis in Esterification.³ The reactions of esterification especially where fatty acids are concerned, exhibit a feature

³ The general problem of catalysis in organic chemistry is a very large one since reactions are as often as not brought about by the influence of catalytic agents of one kind or another. In many reactions water is a catalyst. Metals and metallic oxides are often used to promote reactions in organic as well as inorganic chemistry, but exactly how or why they are effective is not well understood. The choice of a catalyst

which is of both practical and theoretical importance; that is, the formation of esters from acids and alcohols is generally greatly hastened by the presence of an acid, which acts as a catalytic agent. As is true of catalytic agents generally, the reverse reaction of hydrolysis of the ester is also hastened in the same way. The reaction indicated



is reversible and if a mole of water and a mole of ethyl acetate are heated together, the reaction proceeds very slowly until finally an equilibrium is reached in which about two-thirds of a mole of the ester and water remains, while about one-third of a mole of alcohol and acid is formed. Similarly, if a mole of acetic acid and a mole of alcohol are mixed, the reaction eventually reaches the same equilibrium point; about two-thirds of the material is changed into the ester and water and one-third remains as acid and alcohol.

If the ester and water are mixed as above, however, it will take a very long time for the reaction to come to the equilibrium point. It is likely to take months or years at room temperature. The reaction of hydrolysis is especially slow at the start when there is no acid present. As the reaction proceeds acid is formed and this acid speeds up the reaction to some extent. If, instead of simply putting the ester and water together, a small amount of a strong acid like sulfuric acid is also added, the reaction proceeds very much faster and the same equilibrium point is reached in a much shorter time. Likewise, if the alcohol and acetic acid are mixed, the introduction of a strong acid will increase the rate of their reaction and the same equilibrium point is reached much sooner than if the strong acid were absent. Even under the influence of catalytic agents, the reactions of esterification are quite slow and may take hours or days to come to equilibrium at room temperature. If the reacting mixture with

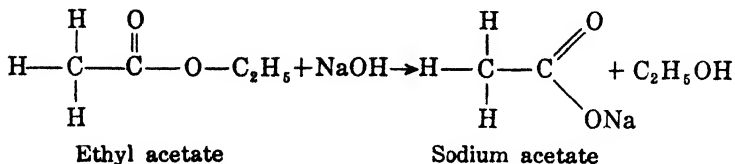
for a particular reaction is most often based upon actual experiment and experience rather than upon theoretical considerations. Many of the applications of catalysis in Organic Chemistry are given in Sabatier-Reid, "Catalysis in Organic Chemistry" (Van Nostrand), but current literature should be consulted also.

the catalyst is kept at its boiling point, the equilibrium may be reached in a few minutes or few hours. The time necessary to reach equilibrium depends on the particular substances involved.

The hydrogen ions produced by the ionization of the acid are responsible for the catalytic effect produced by acids. Thus a strong acid increases the rate of hydrolysis of an ester more than a weak acid, and the effect is directly proportional to the hydrogen ion concentration present. It is thus possible to compare the effects of different acids and by this means determine their comparative strengths. The comparative strengths of different acids as determined in this way agree substantially with determinations made by electrical conductivity methods.

The catalytic effect of alkaline solutions on the hydrolysis of esters is much more striking than that of acids. When the effects of equal concentrations of a strong acid and a strong base are compared at the same temperature, it is found that the hydrolysis often takes place a thousand times as fast in the alkaline medium.

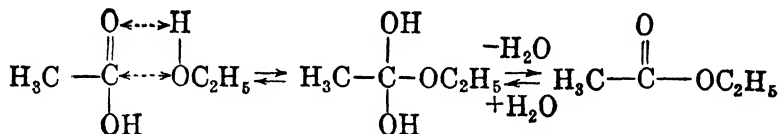
There is one striking difference, however, between alkaline and acid catalysts in the hydrolysis of esters, in that the alkali not only promotes the hydrolysis but also enters into the reaction, neutralizes the acid formed and prevents the reversal of the reaction. Alkaline catalysis is thus more than a simple catalysis; it promotes a one way reaction and *prevents* esterification. The equation for the reaction may be written without reference to the water which presumably enters into hydrolysis and is freed again by neutralization of the acid formed.



It is interesting to note that the hydrolysis of acetic anhydride is catalyzed both by acids and bases, the latter being, as in the case of esters, much more effective. The acid catalysis is not very noticeable except in acetone or other non-aqueous media, while the alkaline catalysis (one way) is very effective in water solution.

It is also noteworthy that hydrolyses of the esters of strong acids such as sulfuric acid and the halogen acids, are not catalyzed by hydrogen ions as are esters of typical organic acids. Alkaline hydrolysis is, however, comparatively rapid. It is thus clear that the esters of strong acids such as ethyl chloride or ethyl sulfate are very closely related in their hydrolysis behavior to the anhydrides of fatty acids.

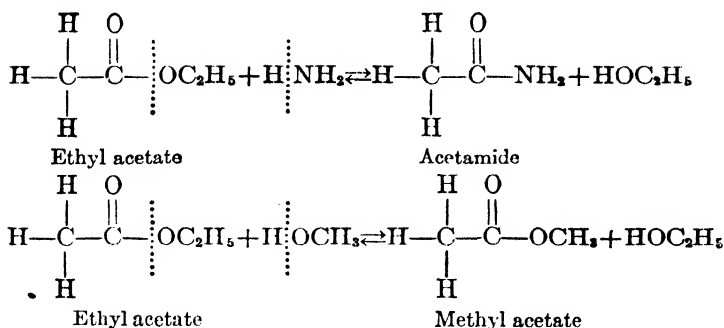
Mechanism of Esterification and Reverse Reactions. While the mechanisms involved in esterification are not known definitely, in spite of extended study on the part of many investigators, the student may be aided by the consideration of a simple mechanism by which such reactions may take place. A common proposal is that in the formation of the ester of a carboxylic acid the alcohol adds to the carbonyl group of the acid, and the product loses water to produce the ester.



The reverse reaction is accomplished by addition of water to the ester followed by the loss of alcohol. This simple picture does not show the role played by catalysts (H^+ and OH^-).

Oxidation and Reduction of Esters. While esters may undergo oxidation, the products are much the same as would be obtained by the oxidation of a mixture of the corresponding acid and alcohol. The reduction of esters is important, however, since acids are very often reduced to aldehydes and alcohols by converting them to esters and then reducing. The unsaturated property of the carbonyl group in esters is more like that in a ketone than that in free (polar) acids. This is correlated with the greater ease in the addition of hydrogen. The first reduction product of an ester presumably is a semiacetal (not isolated) which easily yields an aldehyde.

Reaction with Ammonia, Alcohols, etc. Esters like acid anhydrides undergo ammonolysis, and esters of one alcohol may react with another alcohol as indicated below.



These reactions of the esters, like their hydrolysis, do not take place appreciably in the absence of catalytic agents. The presence of either hydrogen or hydroxyl ions seems to hasten both reactions.

The reactions of esters with alcohols are not generally important. The reaction of ethyl acetate with ammonia pictured above serves as a laboratory method for the preparation of *acetamide*. This reaction does not take place, however, if anhydrous liquid ammonia and ethyl acetate are mixed, but does take place when a strong aqueous solution of ammonia is mixed with ethyl acetate. The difference in the two cases seems to be, that in aqueous solution, hydroxyl ions are present which hasten the reaction.

Fats and Oils. The most important esters occurring in nature are the fats and oils (liquid fats). They constitute a material in which energy is stored by animals and plants. Their abundant occurrence in the flesh of well-fed animals is well known. In plants they are commonly stored in the seeds which often contain a high percentage of fat or oil. This stored food is utilized by the sprouting plant, until it has developed the mechanisms for obtaining energy from other sources.

The fats are not esters of simple alcohols and their study might be postponed were it not for the fact that it is desirable definitely to associate them with the other esters, with which they have so many properties in common. The naturally occurring fats are mixtures of various compounds, and it is impossible

to resolve the mixtures into pure compounds by any known means. The usual method of study involves hydrolyzing the fat mixtures and studying the nature of the fat acids (acids derived from fat) obtained. These can be converted into simple esters and distilled and separated in other ways into pure substances.

The chemistry of natural fats may be summarized very briefly as follows: (1) They are for the most part mixtures of triesters of glycerol, $\text{CH}_2\text{OHCH(OH)CH}_2\text{OH}$. (2) Evidence has accumulated to show that usually the constituents of the mixture are *mixed* esters, that is, more than one kind of acid radical is present in a molecule. (3) Very often one, at least, of the fat acid residues is unsaturated. (4) The acids derivable from fats include members of formic acid series with even numbers of carbon atoms from C_4 to C_{20} or higher, as well as acids with one, two, three, or even more double bonds, hydroxy acids and others. (5) Palmitic, stearic (stē-är'ik) and oleic acids are the most abundant in many common fats. (6) The difference in melting points between fats and oils depends on the extent of unsaturation with the oils being the more highly unsaturated. (7) Often there are associated with fats various related compounds, phospholipides, waxes, sterols, and hydrocarbons.

The glycerol esters of linolic acid, $\text{C}_{17}\text{H}_{31}\text{COOH}$, and linolenic acid, $\text{C}_{17}\text{H}_{29}\text{COOH}$, are present in linseed and other "drying" oils. These acids have two and three pairs of doubly bonded carbon atoms in the molecule, respectively, and the drying of their esters is due to their ability, especially in the presence of catalytic agents or in the light, of taking up (at the double bonds) oxygen from the air to form hard resinous material. This property is, of course, due to the unsaturation of the molecules. The drying of linseed oil is hastened when the oil has been previously boiled with "driers" such as manganese dioxide, litharge, etc. Turpentine also acts as a drier.

The fats, like other esters, undergo hydrolysis and this reaction is used, as has already been mentioned, in the making of soap. When the soap is to be produced the fat is heated with sodium hydroxide which hastens the hydrolysis and converts the fatty acids formed in the hydrolysis into salts. Because of its im-

portance in soap making this reaction has been called *saponification*. Glycerol is formed at the same time and is a by-product in soap manufacture. The hydrolysis may be brought about at higher temperatures by the use of superheated steam, which becomes a simple hydrolysis reaction with no other catalyst present than the hydrogen and hydroxyl ions formed by ionization of the water. Fats can also be hydrolyzed by heating with water in the presence of acids or by special catalytic agents.

Manufacture of Soaps. The most important soaps are those used for cleansing purposes, and there are many different types of these, such as laundry soaps, toilet soaps, shaving soaps, hard water soaps, marine soaps, dye soaps, etc. The nature and use of the soap are dependent upon both the degree of unsaturation and the nature of the metal used to form the salt. For making soaps, and especially for making the cheaper sorts, the fats and oils used are of lower grades, not those which are in demand as edible oils or fats. The most important soap stock is tallow.

In the older process the fat or oil is first brought in melted condition into the soap pan, which may have a sufficient capacity to hold a million pounds of soap. It is first treated with dilute sodium hydroxide solution, and heated and agitated by steam which escapes from coils in the soap pan. The oil becomes emulsified by the soap which is formed or originally added and sodium hydroxide solution (10-20 per cent) is added to the mixture so that there is always an excess of sodium hydroxide, but never a large excess. The heat from both open and closed steam coils keeps the mixture constantly boiling and agitated. The soap is then salted out by adding "pickle" (a saturated solution of salt). The lye layer is eventually drawn off, and from the spent lye glycerol is recovered. To the soap which remains may be added perhaps 50 per cent of its weight of rosin, and sufficient fresh alkali to saponify the rosin. After boiling a sufficient length of time the soap is again salted out and the water layer removed. The soap may then be boiled a third time with 16 per cent sodium hydroxide until complete saponification is assured. When the spent lye has been removed again, the steam is allowed to escape from the coils into the soap. The condensed steam dissolves practically all of the impurities and partially dissolves the soap. After the steam is shut off this final mixture stratifies into two layers, the pure soap floats on a layer of dark-colored solution ("nigre") which contains some sodium hydroxide, soap and impurities. The upper soap layer is then removed and is solidified, cut and made ready for marketing.

In the newer "Twitchell process" the hydrolysis of the fats or oils is brought about in an acid medium and special emulsifying agents (sul-

fonated oils, etc.) are used. In the "Ittner" countercurrent hydrolysis process the fat is split by using water at an elevated temperature without the aid of a catalyst. In both processes fatty acids are produced and separated because of their insolubility. The acids are then saponified with soda ash (Na_2CO_3) which costs about half as much as sodium hydroxide. (See also newer detergents p. 145.)

Hydrogenation of Oils. Vegetable and fish oils consist largely of glycerol esters of higher unsaturated acids. By the use of proper catalysts these esters can be made to combine with hydrogen to form solid or semi-solid fats. These fats are often much more valuable than the original oils, both for soap manufacture and food purposes. The hydrogenation of oils is therefore an important industry.

Various catalysts have been used, the most important of which is finely divided nickel. In preparing the catalyst the nickel may be precipitated in the form of the carbonate on some inert material such as kieselguhr, and after washing, reduced to metallic nickel in an atmosphere of hydrogen at about 300°C . The nickel thus produced is pyrophoric (ignites spontaneously) and must be protected from contact with air. As the success of the operation depends largely on the catalyst, the hydrogen used must be pure, otherwise the nickel may be poisoned by hydrogen sulfide, carbon monoxide, etc. The oil to be hydrogenated is mixed with the catalyst, pumped into a tall iron tank or hydrogenator from which all the air is displaced with hydrogen. The oil is agitated with the catalyst by means of a circulating pump and hydrogen is introduced into the oil under pressure. The pressure used varies, but may be as high as 25 pounds per square inch. The temperature is held at $175\text{--}190^\circ \text{C}$. during the hydrogenation by means of heating coils. When hydrogenation has proceeded far enough the oil is drawn off, separated from the catalyst and allowed to cool and solidify.

For the production of edible fat from cotton seed oil, either of two procedures may be employed. The whole of the oil may be partially hydrogenated, or a part may be completely hydrogenated and mixed with some of the untreated oil. When completely hydrogenated the fat is quite hard and has almost the consistency of wax.

Saponification Number. For distinguishing between various natural fats the *saponification number* of the fat is determined. This number is defined as the number of milligrams of potassium hydroxide which is used up by the saponification of one gram of the fat. The fat is boiled in alcoholic solution containing a known amount of potassium hydroxide (an excess), and after the reaction is complete, the alkali not used up is determined by titration. (It is necessary to use an alcoholic solution because a fat is insoluble in a water solution of an alkali and floats on the surface. It thus comes in contact with the reagent only at the bound-

ary between the fat and the solution. Under such circumstances, reactions take place very slowly.)

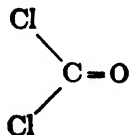
Calculation will show that the saponification number of a fat yielding largely stearic acid is lower than the saponification number of a fat yielding largely palmitic acid because there are fewer molecules in a gram of the fat with the higher molecular weight, and it therefore requires less potassium hydroxide to neutralize the fatty acids formed. The difference is especially great between two fats, only one of which contains butyric acid in combination. If a natural fat consists partly of unsaponifiable matter, this lowers the saponification number. Sterols or solid alcohols such as cholesterol, ergosterol and various phytosterols (of plant origin) are unsaponifiable and are often associated with fats, generally in small amounts.

Iodine Number. The iodine number is arbitrarily defined as the number of centigrams of iodine which may be taken up by one gram of the fat. The iodine is added directly at the double or triple bonds in unsaturated esters. The amount of iodine taken up is then a measure of the amount of unsaturation present in the molecules, and often serves easily to distinguish fats from different sources. Iodine bromide is often the reagent used because of its reactivity, but the results are calculated in terms of iodine.

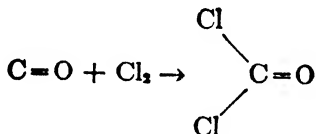
Other Esters Occurring in Nature. Esters are often responsible for the flavors of various fruits, etc. *Methyl butyrate* has the odor of pineapples and is sold as a flavoring material, *isoamyl acetate* similarly has the flavor of pears, *isoamyl isovalerate* resembles apples in odor, *octyl acetate* has the flavor of oranges. Waxes, such as *spermaceti* and *beeswax*, are mixtures of simple esters of higher alcohols and higher fatty acids. *Spermaceti* is largely *cetyl palmitate*, $C_{15}H_{31}COOC_{16}H_{33}$. *Beeswax* contains *myricyl palmitate*, $C_{15}H_{31}COOC_{30}H_{61}$. The waxes, as well as natural products generally, are complex mixtures of different substances.

Esters of inorganic acids, as far as general properties are concerned, are much like the esters of organic acids, and undergo hydrolysis and other reactions in an analogous manner. Catalytic effects (p. 163) and hydrolysis mechanisms are often different (p. 77). The esters of the halogen acids have already been discussed since they are identical with the substances formed by the action of halogens on saturated hydrocarbons or of the halogen acids on unsaturated hydrocarbons.

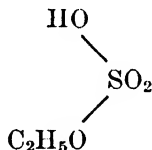
Phosgene or carbonyl chloride may be regarded as the acid chloride of carbonic acid,



and its behavior is in accordance with this relationship. It was the most important poisonous gas used in gas warfare during World War I. It is made by the interaction of carbon monoxide and chlorine in the presence of activated carbon as a catalyst. It finds a number of uses in chemical synthesis.



Ethyl sulfuric acid has already been mentioned. It is an example of a compound which is at the same time an ester and an

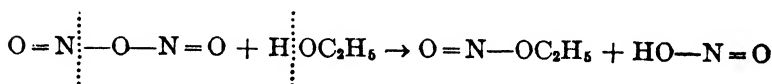


acid. Like other acids it is capable of forming salts; when neutralized with barium hydroxide a *soluble* barium salt is formed and no precipitation results, showing that there are no sulfate ions present in the ethyl sulfuric acid solution. This emphasizes the fact already noted that esters do not ionize. Ethyl sulfuric acid is capable of forming esters with alcohols and by this reaction diethyl sulfate (C_2H_5)₂SO₄ is formed. Both ethyl sulfuric acid and diethyl sulfate, as well as other corresponding alkyl compounds, hydrolyze like other esters, but their hydrolysis is not catalyzed by acids (p. 165).

Dimethyl sulfate is often used as a reagent for the introduction of methyl groups into alcohols (methylation). In the pres-

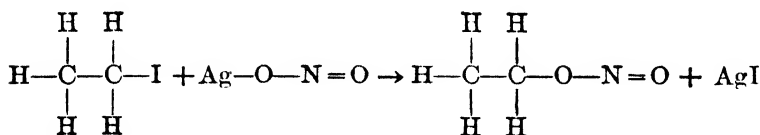
ence of dilute alkali the methyl ether, sodium sulfate and water are formed. This reagent is very poisonous and is dangerous even when it comes in contact with the skin.

Esters of nitric and nitrous acid are of some importance. When nitric acid and ethyl alcohol are mixed,⁴ some oxidation of the alcohol may take place accompanied by a reduction of the nitric acid to nitrous acid, which may also act on the alcohol to form an ester. To avoid the formation of *ethyl nitrite*, *urea* is added. This reacts with the nitrous acid in a manner to be studied later, as fast as it is formed. Ethyl nitrite may be made by the action of sulfuric acid on a mixture of sodium nitrite and alcohol. (Nitrous acid itself is, of course, unstable.) It may also be made by the alcoholysis of nitrous anhydride, N_2O_3 .



Ethyl nitrite

Ethyl nitrite can also be made by the interaction of ethyl iodide and silver nitrite. Nitroethane is also produced by this reaction (p. 213).

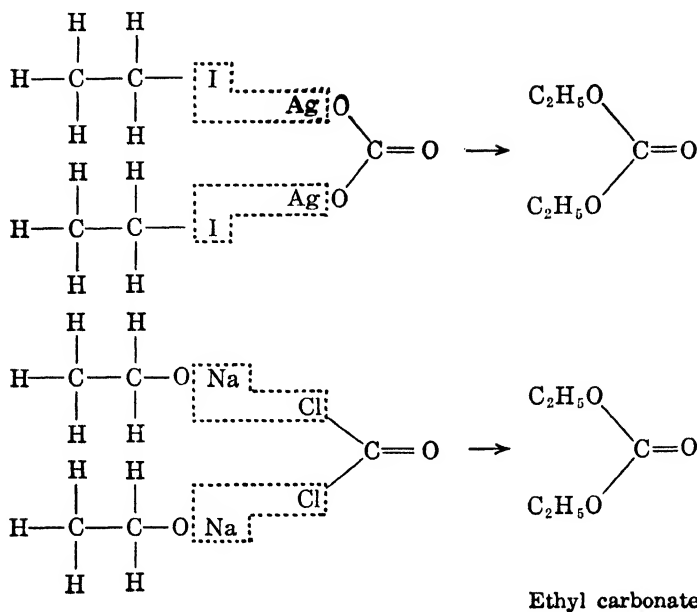


Ethyl nitrite

Ethyl nitrite is the principal constituent of "sweet spirits of niter." *Amyl* (ām'il) *nitrite* is also used in medicine.

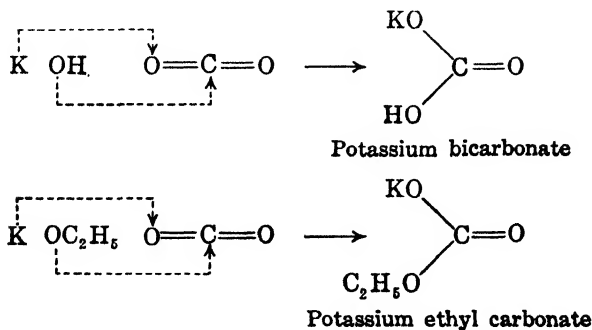
Esters of carbonic acid cannot be made by heating together the acid and alcohol under dehydrating conditions, because carbonic acid is unstable and cannot be obtained except in solution. Diethyl carbonate may be prepared by the action of ethyl iodide on silver carbonate, or by the action of carbonyl chloride on sodium ethylate.

⁴ This reaction must be carried out under definitely controlled conditions, otherwise explosive reactions may take place.



These illustrate indirect methods which may be used for the preparation of other esters.

When carbon dioxide is passed into an alcoholic solution of potassium hydroxide, potassium ethyl carbonate is formed. This is insoluble and precipitates. In this reaction potassium hydroxide and alcohol react to form potassium ethoxide, which adds to the carbon dioxide in a way analogous to the addition of potassium hydroxide to carbon dioxide.



ESTERS OF ACETIC ACID*

Name	Formula	Density	Boiling Point	Solubility in 100 ml. of		
				Water	Alcohol	Ether
Methyl acetate	$\text{CH}_3\text{COOCH}_3$.964 (15°)	57.5	31.9 (20°)	inf.	inf.
Ethyl acetate	$\text{CH}_3\text{COOC}_2\text{H}_5$.900 (20°)	77	8.6 (20°)	inf.	inf.
Propyl acetate	$\text{CH}_3\text{COOC}_3\text{H}_7$.891 (18°)	102	2.36 (20°)	inf.	inf.
Butyl acetate	$\text{CH}_3\text{COOC}_4\text{H}_9$.882 (20°)	125	sl.s.	inf.	inf.
Isobutyl acetate	$\text{CH}_3\text{COOC}_4\text{H}_9$.871 (20°)	116.3	.63 (25°)	inf.	inf.
Amyl acetate	$\text{CH}_3\text{COOC}_5\text{H}_{11}$.866 (25°)	148	.18 (20°)	inf.	inf.
Isoamyl acetate	$\text{CH}_3\text{COOC}_5\text{H}_{11}$.876 (15°)	142.5	.16 (25°)	inf.	inf.
Hexyl acetate (n)	$\text{CH}_3\text{COOC}_6\text{H}_{13}$.890 (0°)	169.2	i.	v.s.	v.s.
Heptyl acetate (n)	$\text{CH}_3\text{COOC}_7\text{H}_{15}$.874 (15°)	191.5	i.	s.	s.

* Several of the esters of acetic acid, notably ethyl, butyl and amyl acetates, are very important technical solvents, particularly for the pyroxylin lacquers. In 1945 15½ million pounds of amyl acetate (90%), 75 million pounds of butyl acetate (90%) and 106 million pounds of ethyl acetate (85%) were produced in United States, largely for use in the lacquer industry.

SIMPLE ESTERS OF METHYL ALCOHOL

Name	Formula	Density	Boiling Point	Solubility in 100 ml. of		
				Water	Alcohol	Ether
Methyl formate	HCOOCH_3	.980 (15°)	32.3	30.4 (20°)	inf.	—
Methyl acetate	$\text{CH}_3\text{COOCH}_3$.964 (15°)	57.5	31.9 (20°)	inf.	inf.
Methyl propionate	$\text{C}_2\text{H}_5\text{COOCH}_3$.915 (20°)	79.9	6.5 (20°)	inf.	inf.
Methyl butyrate	$\text{C}_3\text{H}_7\text{COOCH}_3$.919 (0°)	102.3	s.	inf.	inf.
Methyl isobutyrate	$(\text{CH}_3)_2\text{CHCOOCH}_3$.912 (0°)	92.3	sl.s.	inf.	inf.
Methyl valerate	$\text{C}_4\text{H}_9\text{COOCH}_3$.910 (0°)	127.3	v.sl.s.	inf.	inf.
Methyl isovalerate	$\text{C}_4\text{H}_9\text{COOCH}_3$.901 (0°)	116.7	v.sl.s.	inf.	inf.
Methyl caproate	$\text{C}_5\text{H}_{11}\text{COOCH}_3$.904 (0°)	150	i.	v.s.	v.s.
Methyl caprylate	$\text{C}_7\text{H}_{15}\text{COOCH}_3$.894 (0°)	193	i.	v.s.	v.s.
Methyl caprate	$\text{C}_8\text{H}_{17}\text{COOCH}_3$	—	223.5	i.	v.s.	v.s.
Methyl palmitate	$\text{C}_{15}\text{H}_{31}\text{COOCH}_3$	—	28 (M.P.)	i.	s.	s.
Methyl stearate	$\text{C}_{17}\text{H}_{35}\text{COOCH}_3$	—	38 (M.P.)	i.	s.	s.

FATTY ACID ESTERS OF ETHYL ALCOHOL

Compound	Formula	Density	Boiling Point	Solubility in 100 ml.		
				Water	Alcohol	Ether
Ethyl formate	HCOOC_2H_5	.917	54.4°	11	inf.	inf.
Ethyl acetate	$\text{CH}_3\text{COOC}_2\text{H}_5$.900	77°	8.6	inf.	inf.
Ethyl propionate	$\text{C}_2\text{H}_5\text{COOC}_2\text{H}_5$.896	98°	2.4	inf.	inf.
Ethyl butyrate	$\text{C}_3\text{H}_7\text{COOC}_2\text{H}_5$.886	120°	.68	sol.	sol.
Ethyl isobutyrate	$(\text{CH}_3)_2\text{CHCOOC}_2\text{H}_5$.869	111.7°	s. sol.	inf.	inf.
Ethyl valerate	$\text{C}_4\text{H}_9\text{COOC}_2\text{H}_5$.877	144.5°	i.	inf.	inf.
Ethyl isovalerate	$\text{C}_4\text{H}_9\text{COOC}_2\text{H}_5$.872	134°	i.	inf.	inf.
Ethyl caproate	$\text{C}_5\text{H}_{11}\text{COOC}_2\text{H}_5$.873	167°	i.	sol.	sol.
Ethyl caprylate	$\text{C}_7\text{H}_{15}\text{COOC}_2\text{H}_5$.873	206°	—	—	—
Ethyl caprate	$\text{C}_9\text{H}_{19}\text{COOC}_2\text{H}_5$.862	244°	—	—	—
Ethyl palmitate	$\text{C}_{15}\text{H}_{31}\text{COOC}_2\text{H}_5$	—	24 (M.P.)	i.	sol.	sol.

ESTERS OF INORGANIC ACIDS
(See also table on page 39)

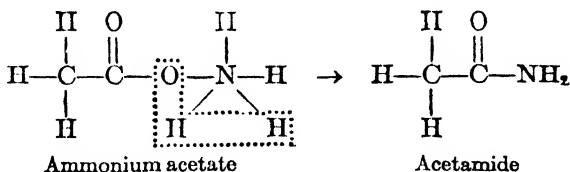
Name	Formula	Density	Boiling Point	Solubility in 100 ml. of		
				Water	Alcohol	Ether
Methyl sulfuric acid	CH_3HSO_4	1.182 (22°)	decomp.	v.s.	s.	inf.
Methyl nitrate	CH_3NO_3	1.991 (15°)	65 exp.	sl.s.	s.	s.
Methyl nitrite	$(\text{CH}_3)_2\text{NO}_2$	1.333 (15°)	- 12	—	s.	s.
Dimethyl sulfate	$(\text{CH}_3)_2\text{SO}_4$	1.046 (16°)	188.5	v.sl.s.	inf.	s.
Dimethyl sulfite	$(\text{CH}_3)_2\text{SO}_3$	1.316 (15°)	126	dec.	s.	s.
Ethyl hydrogen sulfate	$\text{C}_2\text{H}_5\text{HSO}_4$	1.116 (15°)	decomp.	v.s.	s.	s.
Ethyl nitrate	$\text{C}_2\text{H}_5\text{NO}_3$	1.900 (15.5°)	87.6	i.	inf.	inf.
Ethyl nitrite	$\text{C}_2\text{H}_5\text{NO}_2$	1.069 (25°)	17	v.sl.s.	inf.	s.
Ethyl phosphate	$(\text{C}_2\text{H}_5)_2\text{PO}_4$	1.184 (15°)	215	dec.	s.	s.
Ethyl sulfite	$(\text{C}_2\text{H}_5)_2\text{SO}_3$	1.106 (0°)	208	i.; sl.dec.	dec.	—
Ethyl sulfate	$(\text{C}_2\text{H}_5)_2\text{SO}_4$	1.184 (15°)	161	s.dec.	hot	—

Potassium ethyl carbonate is both an ester and a salt. Diethyl carbonate is used as a neutral lacquer solvent and in the synthesis of a wide variety of compounds.

Amides

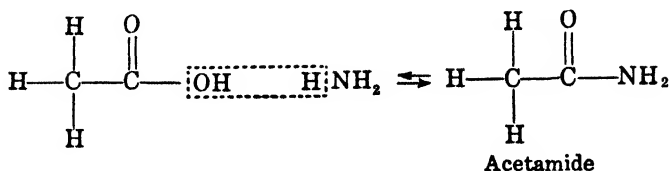
When acyl halides, simple acid anhydrides and esters react with ammonia (ammonolyze) *amides* (äm'id, äm'id)⁵ are formed. Simple amides can therefore be made by any one of these methods. The ammonolysis of an ester unlike the other reactions is slow and definitely reversible, but an ester is often cheaper and more easily handled so they are often used in the laboratory for this purpose.

Amides may be made by still another reaction which is comparable to the common method used for preparing esters, that is, by the direct reaction between the acid and ammonia under dehydrating conditions. Ammonia in the presence of traces of water unites directly with acetic acid (or other acids) to form an ammonium salt. This reaction is an important one, and takes place instantaneously. It may be formulated as a neutralization of the acid by the base, ammonium hydroxide. By heating the salt in a stream of dry ammonia gas, or in an excess of glacial acetic acid, a dehydration takes place with the formation of *acetamide* (äs'ët-äm'id, äs'ët-äm'id).⁵



The net result of the reaction is the same as if ammonia and acetic acid reacted as indicated below.

⁵ The latter pronunciations of these words are often used but are not recommended because it is desirable that the ending *ide* have a pronunciation in accord with other English words. Acid amides are usually named from the corresponding acids by dropping "ic acid" and adding "amide."

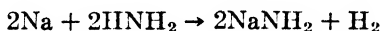


Acetamide may then be regarded as the mixed anhydride⁶ of acetic acid and the weakly acidic ammonia and hence may be classed as an acidic anhydride.

Hydrolysis and Alcoholysis. The hydrolysis of amides is hastened either by the presence of acids or bases, thus the reactions resemble closely the hydrolysis of esters. In the case of amides, however, either an acid or a base causes the reaction to go to completion; if sodium hydroxide is used a sodium salt is formed; if hydrochloric acid is used ammonium chloride is produced. In either case reversal is prevented.

As indicated above, the ammonolysis of an ester is reversible. This is equivalent to saying that alcoholysis of an amide takes place. It is not an important reaction because esters can usually be prepared more easily by other methods.

Acidic and Basic Properties. Ammonia is itself a very weakly acidic substance and shows this property by reacting slowly with metallic sodium to liberate hydrogen.

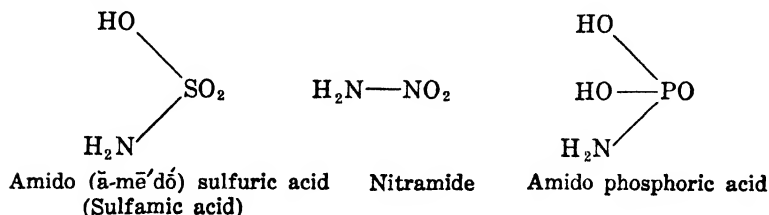


This tendency is very weak, however, even weaker than in alcohols, and the basic character of ammonia is much more prominent, since it forms many important salts with acids which are relatively stable in water solution.

When the acetyl group takes the place of one hydrogen atom in ammonia as in acetamide, this *lowers* the basic property of the ammonia nitrogen and *raises* the acidic property until they are about on the same level. Acetamide is therefore practically neutral; it can act either as a base or as an acid but both tendencies are weak and hence it cannot form salts of either type

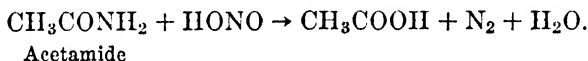
⁶ In a sense this is only a partial anhydride, because there is still hydrogen and oxygen which may be removed in the form of water (p. 202).

that are stable in water. Amides derived from acids which are much stronger than acetic acid have strong enough acidic properties so that stable metallic salts are formed. Though not commonly mentioned in elementary courses amides of inorganic acids are known. Examples are given below.



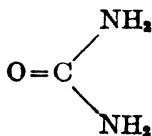
The ammonium salt of sulfamic acid is a valuable flame proofing material for paper and fabrics.

Reaction with Nitrous Acid. The simple amides with which we have been dealing react with nitrous acid, and nitrogen gas is liberated as shown in the equation



This reaction is analogous to the production of nitrogen gas by the reaction of nitrous acid with ammonia; ammonium nitrite is first formed but decomposes into nitrogen and water. The formation of nitrogen from nitrous acid and amides, as from nitrous acid and ammonia, does not take place readily unless the mixture is warmed. The reaction of other ammonia derivatives with nitrous acid will be mentioned later.

Urea is an amide of especial importance. It is the di-amide of carbonic acid and is commonly assigned the structure



- It undergoes hydrolysis like other amides, yielding ammonia and carbonic acid. Its reaction with nitrous acid is analogous to that of other amides. Urea is used industrially in fertilizers, in the production of urea-formaldehyde resins and as a basic material

AMIDES

Name	Formula	Density	Melting Point	Boiling Point	Solubility in 100 parts (20°)		
					Water	Alcohol	Ether
Formamide	HCONH_2	1.134 (20°)	2.5	210.7d	inf.	inf.	sl.s.
Acetamide	CH_3CONH_2	1.139 (15°)	82	222	v.s.	v.s.	sl.s.
Propionamide	$\text{CH}_3\text{CH}_2\text{CONH}_2$	1.033	79	213	s.	s.	s.
Butyramide	$\text{CH}_3(\text{CH}_2)_2\text{CONH}_2$	1.032 (20°)	115.6	216	s.	s.	sl.s.
Caproamide	$\text{CH}_3(\text{CH}_2)_4\text{CONH}_2$.999 (20°)	101.5	dec.	—	v.s.	s.
Caprylamide	$\text{CH}_3(\text{CH}_2)_6\text{CONH}_2$	—	105.9	dec.	v.sl.s.	18.2	s.
Capramide	$\text{CH}_3(\text{CH}_2)_8\text{CONH}_2$.999 (20°)	98.5	dec.	i.	5.9	s.
Lauramide	$\text{CH}_3(\text{CH}_2)_{10}\text{CONH}_2$	—	102.4	dec.	i.	4.7	s.
Myristamide	$\text{CH}_3(\text{CH}_2)_{12}\text{CONH}_2$	—	105.1	217	i.	1.0	sl.s.
Palmitamide	$\text{CH}_3(\text{CH}_2)_{14}\text{CONH}_2$	—	107.0	(12mm) 236	i.	0.5	sl.s.
Stearamide	$\text{CH}_3(\text{CH}_2)_{16}\text{CONH}_2$	—	109.7	(12mm) 204	i.	0.3	sl.s.
Diethyl acetamide	$\text{CH}_3\text{CON}(\text{C}_2\text{H}_5)_2$.925 (8.5°)	78°	(1mm) 185.6	—	—	—
Diacetamide	$(\text{CH}_3\text{CO})_2\text{NH}$	—	78.9	223	s.	—	—
Triacetamide	$(\text{CH}_3\text{CO})_3\text{N}$	—	—	—	—	—	s.

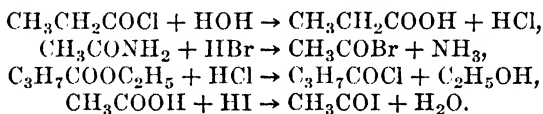
for the synthesis of sulfamic acid. Urea itself and many of its derivatives are of physiological or medicinal importance, and will be discussed in later chapters.

PROBLEMS

1. Which would require more alkali solution to bring permanent neutrality, (1) a gram of glacial acetic acid or a gram of acetic acid anhydride, (2) a gram of acetic acid or a gram of acetyl bromide?

2. What is meant by a catalyst? Does a catalyst ever enter into a reaction? Are catalysts ever "innocent by-standers"?

3. Which of the reactions represented by the following equations would one expect to take place readily in the direction indicated? Why?



4. Why does an ester act extremely slowly with water at first, but after a time react somewhat faster?

5. How many grams of ethyl acetate would constitute a 90 per cent yield if 25 g. of 95 per cent alcohol, 30 g. of pure acetic acid and 2 ml. of conc. H_2SO_4 are the materials used? Is acid or alcohol used in excess?

6. Construct the formulas for nine esters all with the molecular formula $\text{C}_5\text{H}_{10}\text{O}_2$. How many of these may give the iodoform test? How many may give the silver mirror test?

7. Suppose a substance with three carbon atoms and molecular weight 76 reacts with acetyl chloride to form hydrochloric acid and a liquid which on purification proves to have the molecular formula $\text{C}_7\text{H}_{12}\text{O}_4$. What is the molecular formula of the original substance?

8. How could you distinguish by chemical tests between beeswax and paraffin wax?

9. How could you *most easily* distinguish an amide from any other compound already studied?

10. What would be formed by the reaction of nitrous acid on urea?

11. For use in study prepare a table of "acidic anhydrides." In the table give (a) the products of hydrolysis of the anhydrides, (b) a statement as to the acid strength of the acidic substances, (c) state whether or not hydrolysis takes place easily, and (d) indicate what catalysis if any may be used to hasten hydrolysis. Include in the table, ethers, acetals, anhydrides of fatty acids, etc., etc. The table may be extended as new compounds of the same type are studied.

12. A given acid and alcohol at equilibrium are one-half esterified and one-half free which means that the rate of esterification and rate of hydrolysis at equilibrium are exactly equal. Can equilibrium be approached from either direction with equal speed? Why?

13. Thionyl chloride, SOCl_2 , can be used to form an acid chloride. Write a typical equation. (HCl is one product formed.)

14. Acetaldehyde and acetic anhydride react to form a di-ester. Write the equation.

15. From the standpoint of probable reaction mechanism and taking into consideration the structure of salts is it to be expected that an alcohol should react with a sodium salt to form an ester and NaOH?

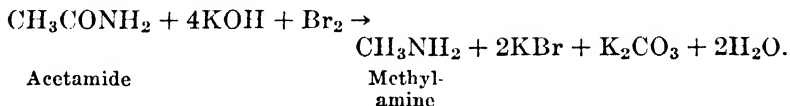
16. Ethyl acetate can be made directly from acetaldehyde by the use of $\text{Al}(\text{OC}_2\text{H}_5)_3$ as a catalyst. Picture the reaction.

17. Although the equilibrium in the reaction between acetic acid and ethyl alcohol to form ethyl acetate is not shifted more than about 1 per cent for a 100° change in temperature why is it desirable to carry out this reaction at a high temperature?

CHAPTER XI

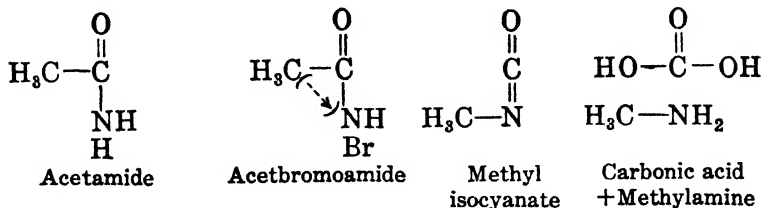
AMINES

When amides are treated with bromine and the product warmed with alkali a series of reactions takes place, known as **Hofmann's reaction**.¹ A simple case is summarized by the equation



It will be noted that so far as the organic compounds are concerned the net result involves the removal of the carbonyl group from its position between the alkyl and amino groups and that the method may serve not only as a means for preparing a typical alkyl ammonia derivative but also for shortening a carbon chain by one link.

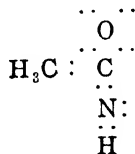
The mechanism of this reaction has been studied extensively and although there is not perfect agreement as to the details, there are certain known facts and plausible interpretations regarding the reaction which are of importance, because they throw light on a number of related *molecular rearrangements*. These events are more common than our study up to this point has indicated. The known facts may be summarized by the following scheme.



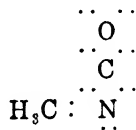
¹ Named for A. W. Hofmann (1818-92), a German chemist who spent considerable of his life in England in the Royal College of Chemistry in London. He was connected with the University of Berlin when he died. His very extensive work was principally concerned with the amines.

The products indicated are all known to be formed and it is possible to start at the second or third step represented and proceed to the formation of methylamine. The unusual feature is involved in the conversion of the acetbromoamide into methyl isocyanate. There are undoubtedly intermediate products formed in this process but they are evidently unstable since they have not been isolated.

The interpretation of this step of the reaction which has evolved through a period of years and which falls in line with available evidence and with the conceptions which we have developed, has been formulated by Whitmore (Jour. Amer. Chem. Soc. 54, 3274, 1932) along with important applications of the same principles to other cases. The first happening in this transformation is the formation of a bromide ion which takes place through the influence of the alkaline medium. This gives rise momentarily to the substance represented below (I) as the other product.



(I)



(II)

This is positively charged but should not be referred to as an "ion" since ions are relatively much more stable; they have completed electron shells and remain indefinitely in solutions associated with ions of the opposite sign. The positive fragment pictured above is obviously an unstable structure because aside from being positive electrically there is a nitrogen present which has only a sextet of electrons. It will therefore decompose or react or rearrange itself so as to yield a more stable product. Nitrogen being more non-metallic than carbon has a stronger pull on electrons; *positive* nitrogen, such as is present here, will have even a stronger pull, so the pair of electrons between the carbon atoms is pulled into the electron shell of the nitrogen and with it follows the methyl group. The nitrogen then shares another pair of electrons with carbon and sometime during the process a proton is lost and the relatively stable neutral methyl isocyanate structure (II) is produced. The hydrolysis of methyl isocyanate in alkaline medium is to be expected as this substance may be regarded as an anhydride of methyl amine and carbonic acid.

It is an interesting point that whenever nitrogen is attached by only one of its valences to a non-metallic element (halogen or oxygen) a negative ion and a positive fragment are likely to be formed (as above). The fragment can then rearrange itself in various ways in different cases.

Ammonium Compounds. Before discussing other methods by which it is possible to prepare ammonia derivatives (amines) it is desirable to review the very interesting valence phenomena concerned with nitrogen and other closely related elements.

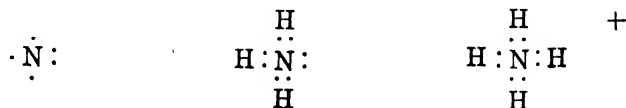
While ammonia is a saturated compound in the sense that it does not add on hydrogen to produce NH_4 or NH_5 , it does show a type of unsaturation. It reacts by addition, with water to form what we commonly call ammonium hydroxide. This substance is unstable, decomposes on evaporation and hence has never been obtained in pure form, though we have adequate evidence of its existence. Most striking is the fact that ammonia reacts with acids by addition to yield the ammonium salts which are stable enough to be purified and are common laboratory reagents. These are unlike most salts, however, in that they break down relatively easily upon heating to yield ammonia and the acids from which they are derived.

With water the situation is exactly analogous throughout, and the differences in stability are only in degree. It reacts with itself to form $(\text{H}_2\text{O})_2$ and it adds to acids to produce hydrates (formulated for example as $\text{HCl} \cdot \text{H}_2\text{O}$ or $\text{H}_2\text{SO}_4 \cdot \text{H}_2\text{O}$). These hydrates are probably similar in structure to ammonium salts but due to their relative instability they are not important "compounds" in the eyes of most chemists and their existence can (for many purposes) be neglected. The more stable oxonium salt derived from dimethyl ether which is an analogous case has already been mentioned (p. 90).

It should be noted that whenever ammonia forms a definite stable addition product, this product readily gives rise to ions. This characteristic is distinctive for ammonia in contrast to the typically unsaturated compounds with which we have dealt. However, other compounds related to ammonia such as phosphine, PH_3 , water and hydrogen sulfide and their derivatives behave in a similar way and show the same characteristic ability to form ionizable addition compounds.

Structure of Ammonium Compounds. The peculiar type of unsaturation exhibited by ammonia and other related compounds is explained with considerable success when the compounds are viewed from the standpoint of their probable electronic structures. A neutral nitrogen atom is composed of a

kernel with a net charge of five positive, surrounded by five electrons in the outer shell. It lacks three electrons of having a stable arrangement of four pairs or an octet. In ammonia, the octet is completed as indicated below.

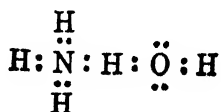


In the structure of the ammonia molecule it will be noted that three pairs of electrons are engaged in holding three hydrogen nuclei but that one pair (on the right in the above diagram) is not so engaged. This pair of electrons is thought to be responsible for the unsaturated properties of ammonia.

The ammonia molecule as pictured above is electrically neutral and since its octet is complete and no double bonds are present it cannot add on hydrogen atoms which are composed of a proton plus an electron. It is, however, easy to picture the addition of a proton (hydrogen ion) to the above molecule in which case we obtain a structure which is similar to that of methane except that it is positively charged rather than electrically neutral.

Since ions of one kind do not occur in solution by themselves, but only along with ions of opposite sign, ammonium ions are always associated with some negative ion. Although it has been common to indicate a valency of five for nitrogen in ammonium salts, actually present ideas of molecular structure are contrary to the idea that the nitrogen in ammonium compounds is ever attached by an ordinary chemical bond to a fifth atom or group.

The idea is fairly well established now that in many cases a hydrogen atom may serve as a loose bond between atoms (p. 126) and accordingly ammonium hydroxide may have the following structure.

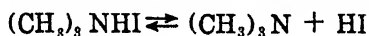
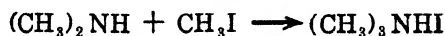
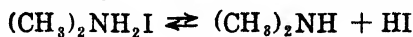
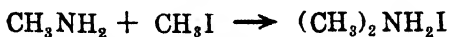
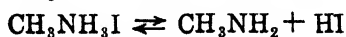
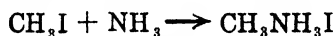


Unless hydrogen bridges exist there seems to be no way in which the hydroxyl can be attached to the ammonium. This point will be mentioned again in a later paragraph.

It will be seen that the above picturization makes clear why the addition compounds of ammonia, unlike addition compounds formed by the typically unsaturated compounds, always undergo ionization. If we look upon the addition of a hydrogen ion to ammonia as a reversible process we find that the thermal decomposition of ammonium chloride (and other ammonium compounds) is to be expected. As long as the hydrogen ion remains attached to the ammonia, the chloride ion is held by electrostatic attraction. As soon as the hydrogen ion is released, chloride ions necessarily lose their previous electrostatic association with the nitrogen.

Formation of Primary, Secondary and Tertiary Amines.

The peculiar unsaturated character of ammonia exhibits itself in its ability to react with the more reactive of the alkyl halides. When ammonia is heated with methyl iodide in alcoholic solution a series of reactions takes place. These consist of addition reactions each followed by a reversible dissociation. The first three pairs of reactions are indicated below.



Methylamine (a primary amine, [ăm'ĕn]) which is formed by the first pair of reactions is very much like ammonia and has the same ability to add methyl iodide. This leads to the formation of dimethylamine, a secondary amine, which in turn reacts again to form trimethylamine, a tertiary amine. It is not possible to stop this series of reactions definitely at any given point but

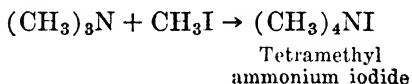
by varying the proportion of the reagents and the reacting conditions it is possible to get a considerable proportion of one product, which is mixed, however, with the others.

The first addition product in each case above is a salt and in general properties is much like ammonium iodide. When treated with caustic alkali they behave like ammonium salts and yield the corresponding amines which are volatile.

The formation of methylamine by the method outlined above involves the ammonolysis of a special type of ester (methyl iodide). The second reaction is similar except that "ammonolysis" takes place with a substituted ammonia—methylamine.

It is probable that the reaction involves first the formation from methyl iodide of an iodide ion and a positive fragment (CH_3), in which carbon has only a sextet of electrons. This reactive fragment adds immediately to the ammonia yielding methylamine. The process can then be repeated with further methyl iodide and methylamine which is formed in the first reaction. Halides other than iodides are not as effective in this type of reaction because they are relatively unreactive.

Formation of Quaternary Ammonium Compounds. Trimethyl amine $(\text{CH}_3)_3\text{N}$ is itself much like ammonia in some respects and is able to react by addition with methyl iodide.



The product formed in this case is much more stable than ammonium salts or other salts mentioned in the previous paragraph. This is due to the fact that whereas each of the other substituted ammonium salts is able to break up into an amine and an acid, this salt in order to decompose must break a carbon-nitrogen bond. Even moderate heating with alkali does not cause it to break down. By the use of silver oxide suspension (equivalent to silver hydroxide) the iodide may be precipitated and tetramethyl ammonium hydroxide is left in solution. Unlike the other substituted ammonium hydroxides this does not break down when evaporated and the solid can be cast in sticks. It is a strong base like sodium hydroxide, as are other quaternary ammonium bases. Quaternary ammonium compounds are finding wide use as cationic germicides, especially in the food industry.

Basic Properties of the Substituted Ammonium Bases.

The amines, like ammonia, when dissolved in water form weakly basic solutions. The weakness of the bases is shown by the fact that it is impossible to prepare a solution of any of them in which there is a high hydroxyl ion concentration. The cause of the weakness of ammonium hydroxide is due partly to its tendency to decompose into ammonia and water, but also due to the fact that the hydrogen bridge which apparently exists is not the type which allows free ionization; the hydroxyl ion remains to a considerable extent undissociated. The values for the "ionization constants" of the bases given in the table below are calculated upon the assumption that the hydroxides do not break down into amine and water at all. Inasmuch as this breaking down is known to happen the "true" ionization constants are larger than the values given though they are thought to be in the same order. Practically these "true" constants are not as valuable as the "apparent" constants.

APPARENT STRENGTHS OF AMMONIUM BASES

	"Ionization Constants"	Per cent ionised in .1 N solution
Ammonium hydroxide000018	1.3
Methylammonium hydroxide0005	6.9
Dimethylammonium hydroxide000535	7.1
Trimethylammonium hydroxide000059	2.4
.....		
Ethylammonium hydroxide00056	7.2
Diethylammonium hydroxide00126	10.7
Triethylammonium hydroxide00044	6.4
.....		

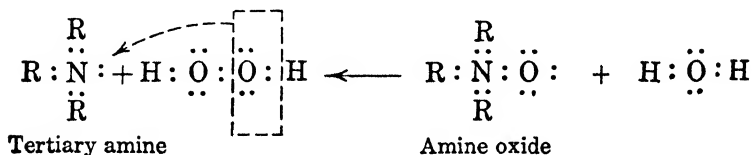
It will be noted that the alkyl ammonium bases are in general stronger than ammonium hydroxide. This is in keeping with the fact that alkyl groups decrease acid properties (as in the fatty acids) and therefore increase basic properties.

The quaternary ammonium bases present quite a different picture, because they are highly ionized. This is probably best explained by the fact that in the quaternary bases there is no possibility of a "hydrogen bridge" (such bridges do not form with hydrogen that is attached to carbon) and therefore there is

no way in which the hydroxyl ion can be attached to the cation to form an undissociated molecule.

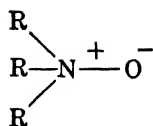
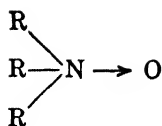
In compounds which have the ammonium type of structure it makes no difference what alkyl groups are present or whether some other element such as phosphorus, arsenic or antimony takes the place of nitrogen, the tetra substituted bases are all strong evidently because there is no place for the hydroxyl ion to become attached. In the family of compounds ammonia, phosphine, arsine and stibine the basic properties decrease to the vanishing point in the case of the latter two, but *tetra*-methyl phosphonium, arsonium and stibonium hydroxides are all *strong* bases.

Amine Oxides, Co-ordinate Valences. Tertiary amines react with hydrogen peroxide to form amine oxides. In terms of electron structures such a reaction can be represented thus:



It will be noted that although the octets are all satisfied in an electrically neutral structure (amine oxide) the situation is unusual in two obvious respects, first oxygen appears to be monovalent, and second the electron pair constituting the N-O bond is furnished entirely by the nitrogen rather than in the usual way by both atoms involved.

Furthermore the oxygen *possesses* six electrons and shares *two* (p. 12 hence is negative, whereas nitrogen shares eight and possesses none and hence is positive. This positive-negative condition within the molecule produces a high dipole moment. The presence of high dipole moments is definitely correlated with the presence of valence bonds of the type under discussion. The bonds are known as *coordinate* valences to distinguish them from ordinary covalent bonds, and are also sometimes called *semipolar bonds*. They may be represented in either one of two ways illustrated below. In the first, which is convenient and widely used, the arrow points away from the element which contributes both electrons. The second formula emphasizes the fact that the structure is exactly as if there were two bonds between the nitrogen and oxygen, one covalent and one electrostatic (completely ionized). The electrostatic bond cannot become covalent (forming a double bond) because there is not room in the nitrogen shell for 10 electrons.



The amine oxides like the amines are basic in character. They can lose the oxygen to reducing agents.

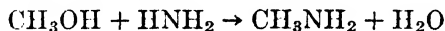
Other Methods of Preparing Amines. It is possible to prepare the various amines by different methods some of which involve compounds which are as yet unfamiliar to the student.

Methyl amine can be prepared by the interaction of formaldehyde and ammonia or ammonium chloride.



At higher temperatures di- and tri-methylamines are formed from the same reagents.

The same amines can be produced by passing the vapors of methanol and ammonia over alumina or silica catalysts at about 300° or by heating the two reagents together under pressure in the presence of zinc chloride.



These methods are also applicable to a limited extent to homologous amines that are subject to the limitation in all cases that primary, secondary and tertiary amines are formed in succession and it is not possible to obtain one amine directly without some admixture of the others.

The formation of methyl amine by the reaction indicated above suggests the fact that the amines are mixed anhydrides of alcohol and ammonia. In conformity with the fact that they are anhydrides of very weakly acidic substances the amines do not ordinarily undergo hydrolysis. In this respect they resemble ethers which are the anhydrides of alcohols.

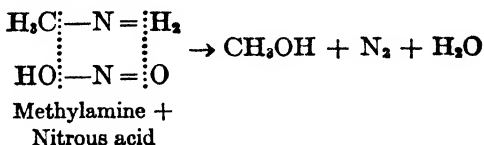
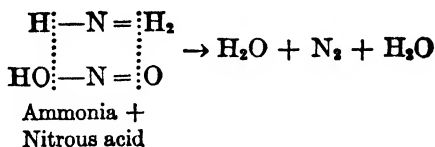
Separation of Primary, Secondary and Tertiary Amines. The fact that primary, secondary and tertiary amines are formed together under various conditions suggests the desirability of being able to separate them one from the other. There is no simple way of making a complete separation, but by sacrificing

the primary amine (and obtaining it in some other way, *e.g.*, by Hoffman's reaction), the secondary, tertiary and quaternary compounds can be separated and purified.

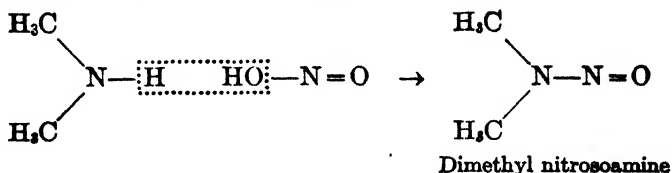
The quaternary compounds can be separated from the others by making use of the fact that the base does not volatilize when an alkaline solution is distilled. Nitrous acid is used to separate the secondary and tertiary amines, and at the same time to destroy the primary amine and any unchanged ammonia.

When nitrous acid is used as a reagent, sodium nitrite is most often introduced into a solution of the amines containing an excess of some acid. The acid reacts with the nitrite to generate nitrous acid in the solution in which it is to be used. Nitrous acid may also be introduced in the form of its anhydride, N_2O_3 . In picturing the reactions that take place it is most convenient simply to indicate the reaction as taking place between the amine itself and free nitrous acid.

Ammonia with nitrous acid first produces ammonium nitrite which is unstable and decomposes into nitrogen and water. In a similar manner methylamine and nitrous acid give methyl alcohol, water, and nitrogen.

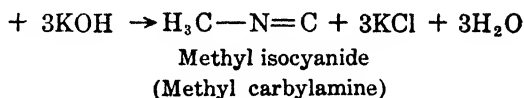
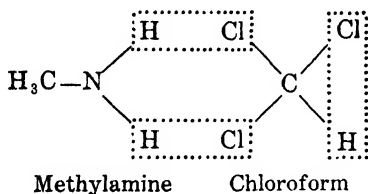


With secondary amines nitrous acid reacts to form an anhydride-like substance called a *nitrosoamine*.



The nitrosoamine is a neutral volatile substance, which can be removed from the solution either by passing steam into the acid mixture which removes it from the non-volatile salts, or by extraction with ether which accomplishes the same result. The nitrosoamine may then be recovered from the condensed steam or the ether solution, and can be hydrolyzed in the presence of an acid to produce the original amine and nitrous acid. Tertiary amines are not affected by nitrous acid except to form the unstable nitrite which is easily convertible into the original amine, and nitrous acid.

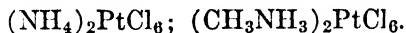
The *isocyanide* or *carbylamine* reaction (p. 205) may be used as a test for primary amines. When a primary amine is warmed with an alkaline solution containing chloroform, an isocyanide is formed and it may be recognized by its characteristic disagreeable odor. The reaction may be pictured in the following manner.



This reaction cannot take place with a secondary or tertiary amine. Isoocyanides will be studied later.

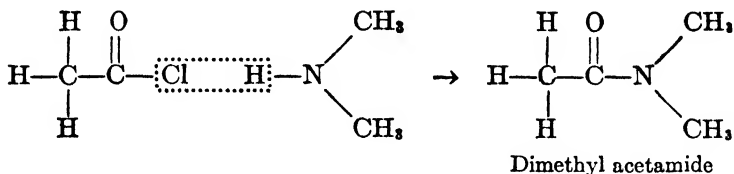
Salts of Amines. Amines form salts with all types of acids. In solution the salts of the strong acids give an acid reaction due to hydrolysis. Amines which are used as reagents in laboratories or that have technical or other uses are often handled and sold in the form of their salts rather than as free amines. With chloroplatinic acid, H_2PtCl_6 , amines yield salts which may be utilized in their study, particularly to determine equivalent weight. When the chloroplatinic acid salt of an amine is ignited a residue of pure platinum results and the weight of platinum obtained from a weighed sample of a salt makes it possible to

calculate the probable molecular weight of the amine. The salts are analogous to ammonium chloroplatinate, as shown by the following formulas.



Complex gold salts may be prepared and used in a similar way.

Reactions of Amines with Acid Anhydrides, etc. The striking similarity of the amines to ammonia which has already been noted is borne out by the fact that the reactions of primary and secondary amines with acetyl chloride, acetic anhydride, etc., are similar to that of ammonia with these reagents.



The products formed by these reactions are substituted amides. Tertiary amines which have no hydrogen attached to the nitrogen cannot react in this way.

Occurrence in Nature. The alkyl amines are occasionally found in nature, and more complex amines are of considerable importance. All of those substances which have the amino (ă-mě'nó) group (NH_2) in their structures are related to the amines, and included in this group are some of the most important compounds from the standpoint of biology, including the very complex compounds known as proteins.

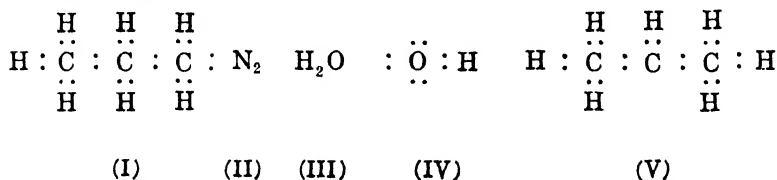
The dry distillation of nitrogenous organic matter often produces alkyl amines in varying amounts. The residue from the fermentation of beet molasses, for example, yields an impure product known commercially as "trimethylamine," which contains a large proportion of this substance. The simple amines have a fish-like odor, and trimethylamine can be obtained from herring brine. Some of the simpler as well as more complex amines are formed by the action of bacteria on various protein materials. Amines (including alkaloids) are often found in plants, and certain poisonous amines are present in various fungi, for example, in ergot (a fungous growth which attacks certain

grains), and in poisonous mushrooms. Some of the more important complex amines are related to the proteins.

Higher Amines. The amines form a homologous series and while the methyl substituted amines have been used as illustrations, the higher amines such as the ethyl and propyl substituted amines, etc., may be prepared by similar methods and have properties similar to the simpler amines. There are primary, secondary, and tertiary amines and also quaternary ammonium compounds which have higher alkyl groups in their structure. In addition there are mixed amines such as methyl ethyl amine, ethyl dimethyl amine, etc.

In the reactions of the higher amines with nitrous acid certain interesting arrangements take place which fall in line with our previous discussion on page 186. Even propyl amine when treated with nitrous acid yields some *isopropyl* alcohol along with *n*-propyl alcohol.

It is supposed that the nitrous acid reaction results in stripping off the nitrogen with the bonding pair of electrons which held it to carbon, yielding momentarily the products (I), (II), (III) and (IV) indicated below.

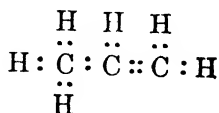


The positive fragment (I) is very reactive and may add the hydroxyl ion to produce *n*-propyl alcohol. However, before this can take place it seems probable that the positive carbon [in (I)] may pull a pair of electrons from the center carbon and with them a proton. This yields another positive fragment (V) which by combination with the hydroxyl ion will yield *isopropyl* alcohol. These positive fragments are probably of extremely short "life," possibly shorter than that of the free radicals mentioned previously.

There are several questions which naturally arise from a consideration of this proposed mechanism: Why should these positive fragments become linked with hydroxyl ions when there are other negative ions in much higher concentration in the solution (Cl^- and NO_2^-)? If the mechanism is correct the answer lies in the probability that hydroxyl ions are *formed by the reaction* in the immediate vicinity of the fragment and hence are more likely to be added than other ions. A second

point in this connection is that in the one analogous reaction of this type which has been thoroughly investigated (butyl amine plus nitrous acid) both chlorides and nitrites *are formed* in appreciable amounts simultaneously with the alcohols.

If the positive fragments indicated above are formed it is obvious that they might become stabilized by the loss of a proton (to the hydroxyl ion). This would result in the formation of propylene.

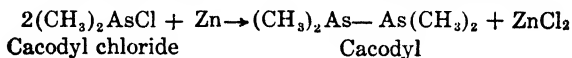
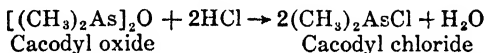
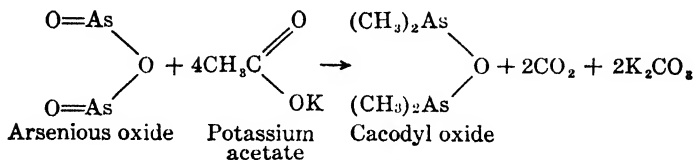


Actually propylene is a prominent product of the reaction. In some analogous cases the unsaturated hydrocarbons are formed in larger amounts than alcohols. On the basis of being able to explain the formation of the various products in a plausible way, this proposed mechanism is highly satisfactory.

ALIPHATIC AMINES

	Formula	Density	Boiling Point	Solubility in 100 ml.		
				Water	Alcohol	Ether
Methylamine ..	CH_3NH_2	.669 (-10.8°)	-6.7	1150 cc. (12°)	s.	inf.
Ethylamine ..	$\text{C}_2\text{H}_5\text{NH}_2$.689 (15°)	16.6	inf.	inf.	inf.
Propylamine ..	$\text{CH}_3\text{CH}_2\text{CH}_2\text{NH}_2$.719 (20°)	49	s.	inf.	inf.
Isopropylamine	$(\text{CH}_3)_2\text{CH}-\text{NH}_2$.690 (20°)	34	inf.	inf.	inf.
Butylamine n..	$\text{CH}_3(\text{CH}_2)_3-\text{NH}_2$.740 (20°)	78	v.s.	s.	s.
Isobutylamine	$(\text{CH}_3)_2\text{CH}-\text{CH}_2\text{NH}_2$.735	68	inf.	inf.	inf.
Sec.-butylamine	$\text{CH}_3\text{CH}(\text{NH}_2)-\text{CH}_2\text{CH}_3$.724 (20°)	63	inf.	inf.	inf.
Amylamine ...	$\text{CH}_3(\text{CH}_2)_4-\text{NH}_2$.766	104	s.	s.	inf.
Hexylamine ..	$\text{CH}_3(\text{CH}_2)_5-\text{NH}_2$	—	132.7	v.s.	inf.	inf.
Heptylamine ..	$\text{CH}_3(\text{CH}_2)_6-\text{NH}_2$.78	156.9	v.s.	inf.	inf.
Octylamine ...	$\text{CH}_3(\text{CH}_2)_7-\text{NH}_2$.78	180	31.5 (20°)	inf.	inf.
Dimethylamine	$(\text{CH}_3)_2\text{NH}$.687 (-6°)	7.2	v.s.	s.	s.
Diethylamine .	$(\text{C}_2\text{H}_5)_2\text{NH}$.712 (15°)	56	v.s.	s.	s.
Trimethylamine	$(\text{CH}_3)_3\text{N}$.662 (-5°)	3.5	v.s.	v.s.	s.
Triethylamine	$(\text{C}_2\text{H}_5)_3\text{N}$.733 (15°)	89	1.5 (20°)	inf.	inf.

Cacodyl (kăk'ô-dîl) oxide and cacodyl (from Gr. meaning ill smelling) are compounds of arsenic which have some historic interest, because Bunsen ² thought that in preparing cacodyl he had prepared a radical in the free unattached condition. It has since been shown that the so-called free radical has twice the molecular weight of the true radical and consists of two attached radicals just as an ethane molecule consists of two joined methyl radicals. Cacodyl oxide was made by the dry distillation of a mixture of potassium acetate and arsenious oxide and is the principal product formed. This reaction, like others involving high temperature decompositions, is hard to picture definitely. The following equations show how cacodyl oxide and cacodyl may be formed.



PROBLEMS

1. One gram of methylammonium chloride is dissolved in water, made alkaline with sodium hydroxide solution, and distilled without loss into 50 ml. of 1 N hydrochloric acid solution. How much 0.5 N sodium hydroxide solution should be required to bring the resulting solution to neutrality?

2. Suppose 0.2 g. of a sample of sodium nitrite is treated in acid solution with a primary amine and 500 cc. of nitrogen (standard condition) is obtained. What is the purity of the sodium nitrite?

3. Amines combine with chloroplatinic acid (H_2PtCl_6) to give compounds of the general type $(\text{R}_3\text{NH})_2\text{PtCl}_6$. (R represents alkyl groups or hydrogen.) .528 gram of the chloroplatinic derivative of a simple

² R. W. Bunsen (1811-99) lost the use of his right eye in an explosion of cacodyl cyanide. Thereafter he worked in the field of inorganic chemistry where he made outstanding contributions to petrology and gas analysis and was a pioneer with Kirchhoff in spectroscopic analysis. The common laboratory burner bears his name. He held a professorship at Heidelberg for many years. Cacodyl was isolated in 1842.

amine on ignition left a residue of .195 gram of platinum. What is the molecular weight of the original amine?

4. Compare the neutralizing power of one gram samples of the various simple amines and determine which will neutralize the most acid. Do the same differences hold in case you compare the neutralizing power of one liter gaseous samples of the amines?

5. Write out the molecular and structural formulas for the following amines: (a) methylethylamine, (b) isopropylamine, (c) trimethylamine, (d) *n*-propylamine. What relationship do these compounds bear to each other? Which react with nitrous acid? Which cause an evolution of gas when reacting with nitrous acid?

6. Which types of amines would you expect to react with Grignard reagents?

7. It will be noted that in the treatment of an amide with bromine and alkali, the resulting product has one less carbon atom than the original amide. How would it be possible to prepare acetic acid using propionic acid as the starting material?

8. How could propionic acid be prepared starting with acetic acid, making use of a Grignard synthesis?

9. Show how methyl alcohol could be prepared starting with acetamide. How could the same reactions along with others be utilized in preparing (a) formic acid from acetic acid, (b) acetaldehyde from propionaldehyde?

10. How could isopropyl alcohol be prepared starting with isobutyric acid?

11. What simple chemical test would serve to distinguish an amide from an amine? What physical difference is there between the lower members of the amine and amide series?

12. Designate each of the following as a primary, secondary or tertiary amine: (a) tert. butyl amine, (b) dibutyl amine, (c) sec. butyl *n*-butyl amine.

13. How can isopropyl alcohol be prepared starting with propionic acid?

14. When complex amines are treated with nitrous acid unsaturated compounds result. How? What is the simplest unsaturated compound which could theoretically be produced in this way?

15. Work out a possible course of the reaction between ammonia and formaldehyde, making use of the unsaturation of formaldehyde and bearing in mind the possibility of intermolecular oxidation reduction reactions (p. 103).

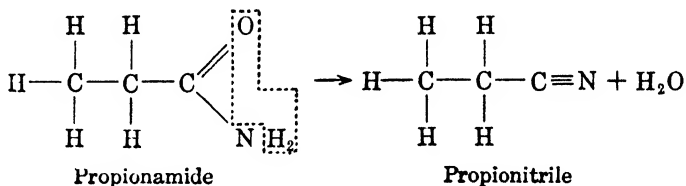
16. Ammonolysis of alkyl halides or alkyl sulfates yields alkyl amines. Ammonolysis of typical esters does not. What products are formed? Can you be sure that in the hydrolysis of a typical ester water does or does not react in a fashion analogous to ammonia?

CHAPTER XII

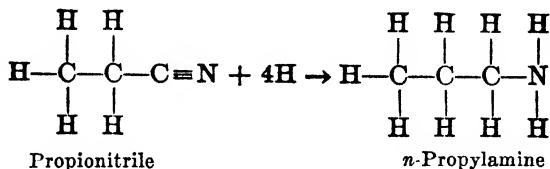
NITRILES, CYANATES, AND OTHER NITROGEN COMPOUNDS

Nitriles

When a simple amide is heated with phosphorus pentoxide, a dehydration takes place, which for propionamide is simply pictured by the following equation.

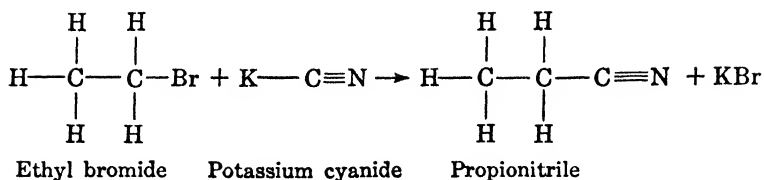


That the substance formed by this reaction has the structure indicated is shown by the fact that it may be reduced to *n*-propylamine. This is easily pictured as follows, in which the triple bond represented as existing between the carbon and nitrogen takes up four hydrogen atoms analogous to the way in which acetylene does (p. 60).



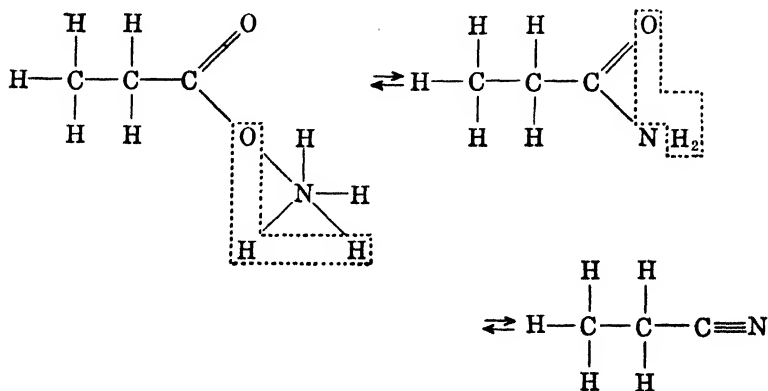
When ethyl bromide is heated with potassium cyanide, the same compound called propionitrile¹ is formed as the principal product. This reaction must take place in the following manner.

¹ The nitriles (s. nī'trīl, nī'trīl) are often called *alkyl cyanides* (propionitrile, propanenitrile = ethyl cyanide) because of their preparation from and resemblance to metal cyanides.



It will be noted that in this reaction a substance with two carbon atoms is converted into a substance with three carbon atoms. This is one of the methods by which a carbon chain can be lengthened. The propionitrile can be converted into propionic acid (ammonium salt) as indicated in the reverse reaction below. It can also be reduced and the propylamine formed yields propyl alcohol on treatment with nitrous acid. This would constitute a good general method for passing from one alcohol to the next higher homolog were it not for the molecular rearrangements which are likely to take place (p. 197) in the case of the higher amines.

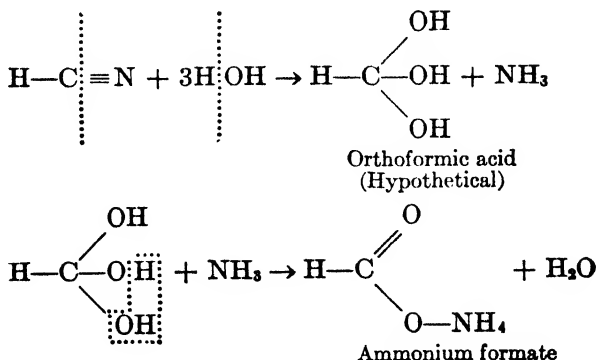
Hydrolysis of Nitriles. Propionitrile may be regarded as the ethyl ester of hydrocyanic acid, and as such might be expected to undergo hydrolysis to form alcohol and hydrocyanic acid. Another reaction than this one takes place, however. Propionitrile may also be regarded as an anhydride of ammonia and propionic acid, and may be made by successive dehydration of ammonium propionate. It hydrolyzes in accordance with this latter relationship.



The failure of propionitrile to hydrolyze like other esters may be correlated with the fact that hydrocyanic acid is an extremely weak acid ($K_a = 7.2 \times 10^{-10}$) and its esters might therefore be expected to be unreactive. By reacting in the other way a much stronger acid is produced by the hydrolysis namely propionic acid ($K_a = 1.34 \times 10^{-5}$).

The hydrolysis is perhaps the most important reaction of the nitriles and from them by complete hydrolysis ammonium salts of fatty acids are obtained. In this hydrolysis the amides are formed as intermediate products so that the series of reactions represented above can be made to take place in the opposite direction. The hydrolysis of a nitrile like that of an amide is hastened by the presence of either an acid or an alkali.

Hydrocyanic acid itself is capable of hydrolysis in a manner similar to the other nitriles and since it produces ammonium formate on hydrolysis, it is the nitrile of formic acid. The hydrolysis of hydrocyanic acid or other nitrile may be pictured as taking place by the complete breaking of the triple bond by an addition of three hydroxyl groups to the carbon atom and three hydrogen atoms to the nitrogen, followed by the loss of a molecule of water by the carbon compound and a neutralization of the acid by the ammonia. The manner of splitting of the triple bond indicates that nitrogen is "negative" with respect to the carbon.



Double Cyanides. When potassium cyanide is added to a silver nitrate solution, silver cyanide is precipitated, and has an

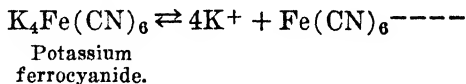
appearance similar to silver chloride. The addition of more potassium cyanide, however, dissolves the precipitate forming a soluble double salt $\text{KCN} \cdot \text{AgCN}$ or $\text{KAg}(\text{CN})_2$. Such a solution furnishes a very low concentration of silver ions and when silver is electroplated from it a very even coat is formed.

Sodium or potassium cyanide in the presence of air or other oxidizing agent dissolves metallic gold, because of the formation of soluble double cyanides of gold and sodium (or potassium).

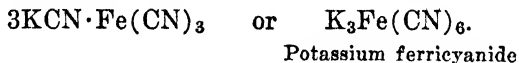


This reaction is the basis of the cyanide process of extracting gold from ore and a solution containing this complex salt is used for gold plating.

The *ferrocyanides* and *ferricyanides* are somewhat familiar to the student of inorganic chemistry, because they are used in analytical tests. When potassium cyanide is added to a solution of a ferrous salt, a precipitate forms which, like the silver cyanide mentioned above, dissolves in an excess of potassium cyanide. This is due to the formation of a double salt, the formula of which is sometimes represented $4\text{KCN} \cdot \text{Fe}(\text{CN})_2$. This formula might be taken to indicate a somewhat indefinite combination of the two substances. A solution of this substance does not, however, contain cyanide ions nor ferrous ions, thus showing that a definite chemical reaction has taken place between the two salts. Potassium ions are present as well as ferrocyanide ions and salts containing these ions may be precipitated from the solution by appropriate reagents.



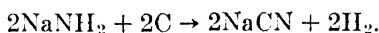
With ferric salts a similar result is obtained, the complex salt may be represented by the following formulas:



When a solution of sodium or potassium ferrocyanide is treated with an excess of ferric chloride or other ferric salt, the

ferric ion from the ferric chloride combines with the ferrocyanide ion of the complex salt forming ferric ferrocyanide, which is *Prussian blue*. The picturing of the structure of the double cyanides by means of structural formulas has not been accomplished successfully because what may be termed secondary valence forces come into play and these cannot be formulated in the usual way.

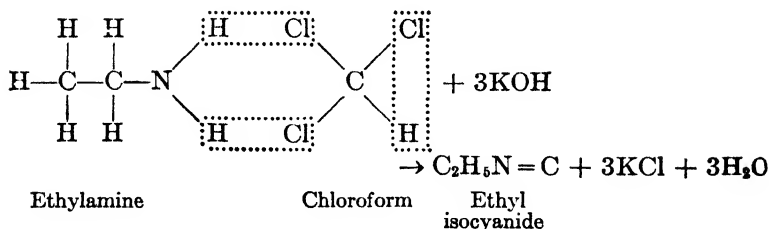
An important method for the production of sodium cyanide involves introducing ammonia into a mixture of hot charcoal and melted sodium. Sodium amide is first formed and reacts with the carbon as indicated



Cyanides find their principal uses in extraction of gold from its ores, as a fumigant for fruit trees, etc., and in silver and gold plating. All of the metallic cyanides are very poisonous; the alkyl cyanides are much less so.

Isocyanides ²

The reaction between chloroform and a primary amine in the presence of an alkali has already been mentioned since it is sometimes used as a test for a primary amine.

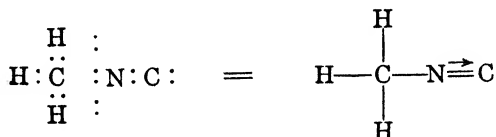


The reaction may be pictured in this way in which case the formula for the product (an isomer of propionitrile) seems plausible

² For some obscure reason the International Union of Chemistry (I.U.C.) has ruled that the name *carbylamine* should be used for compounds of this type. It is more common, however, to call them isocyanides or isonitriles, i.e.: $\text{C}_2\text{H}_5\text{NC}$, ethyl isocyanide, propionisonitrile, ethyl carbylamine.

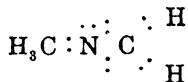
in view of the fact that there are other compounds in which carbon appears to be bivalent³ (carbon monoxide is one) and which have properties in common with the isocyanides. Such compounds show unsaturation and when addition takes place, two atoms become attached to the previously "bivalent" (bī-vā'lēnt) carbon.

The complete structure of alkyl isocyanides (isonitriles) presents an interesting problem, inasmuch as using older valence conventions either nitrogen must be pictured with a valence of five or else carbon with a valence of only two. Either of these suggestions demands further clarification in terms of modern conceptions. The structure of methyl isocyanide is probably best represented as

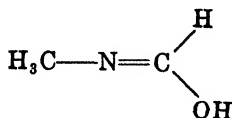


It will be noted that in the first formula all electron shells are satisfied but that carbon shares six and possesses two (hence is negative), while the nitrogen shares eight and possesses none and hence is positive.

The reactive point in the molecule is the lone pair of electrons on the carbon (carbon usually shares all eight electrons) so that when methyl isocyanide is reduced the first product probably has the structure



This adds further hydrogen by breaking a covalent bond to yield dimethyl amine $\text{H}_3\text{C}-\text{NH}-\text{CH}_3$. The first step in hydrolysis may involve the addition of H and OH to the terminal carbon atom in the same way yielding

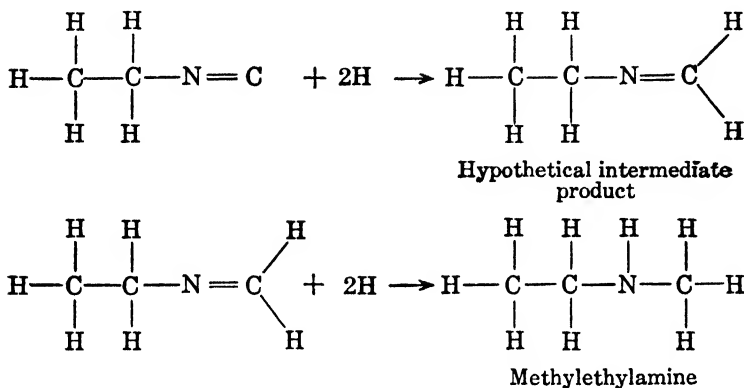


which on complete hydrolysis yields methyl amine and formic acid (which immediately interact to form the salt).

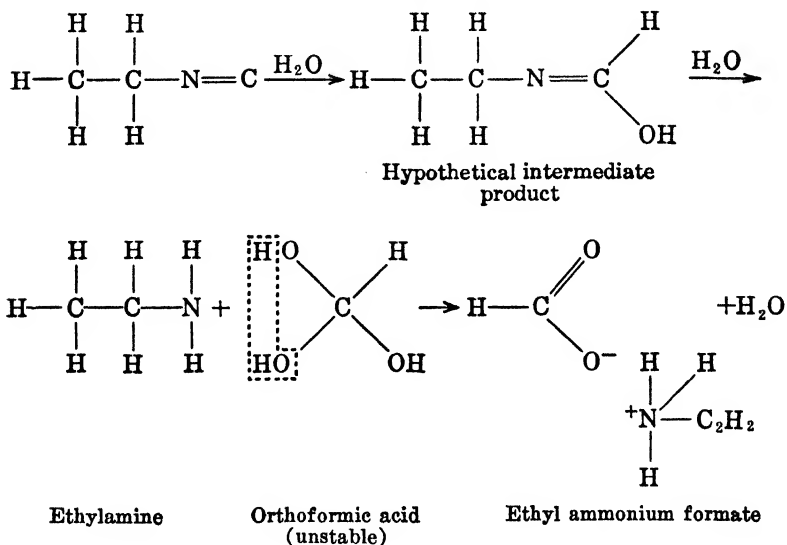
³ J. U. Nef (1862-1917), for years Chairman of the Chemistry Department of the University of Chicago, was largely responsible for establishing the idea of bivalent carbon on a firm basis. He presented evidence bearing on this point in 1893 and the years following.

The coordinate valence conception therefore interprets successfully the apparent bivalent carbon condition.

When ethyl isocyanide is reduced, methylethylamine is produced, and this may be accounted for in the following manner.



Ethyl isocyanide also undergoes hydrolysis forming ethylamine and formic acid which unite to form ethyl ammonium formate. This behavior is in accord with the structure given above, and may be pictured as follows:



Simultaneous Formation of Nitriles and Isocyanides.

When ethyl bromide and potassium cyanide are heated together, the principal product formed is propionitrile, C_2H_5CN , but there is also formed a small amount of ethyl isocyanide, C_2H_5NC . When silver cyanide is substituted for potassium cyanide in this reaction the principal product is *ethyl isocyanide* and some propionitrile is also formed. The difference exhibited here between sodium and silver cyanides is shown several times in the reactions between alkali derivatives on one hand and heavy metal derivatives on the other, with organic compounds.

The phenomenon just cited is nicely interpreted in terms of electronic structures. The cyanide ion and isocyanide ion are thought to have identical structures so that no distinction exists between sodium



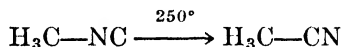
cyanide $Na\overset{+}{C}\overset{-}{N}$ and $Na\overset{+}{N}\overset{-}{C}$ since the substance is a highly ionized salt and the $C\bar{N}$ combination reaches the same stable structure in both cases. Silver cyanide, however, is one of the few salts that is but feebly ionized ($Hg(CN)_2$ is another), and is thought to exist undissociated in the form indicated above. (The pair of electrons on the left are in the shell of the silver atom. Larger atoms may have room in their completed shells for extra electron pairs.) The silver might be attached to the nitrogen but it has been calculated on the basis of the charges on the kernels and the distances between them that the one represented should be the more stable combination.

When an alkyl halide reacts with *silver cyanide* (undissociated) the alkyl group can become attached only on the nitrogen atom (analogous to the formation of a quaternary ammonium ion from a tertiary amine). The silver ion then drops off to become associated with the iodide ion and the alkyl isocyanide results. When the alkyl halide encounters *cyanide* ions (from $NaCN$ for example) the situation is different, in that two positions can be taken by the alkyl group: it can attach either to nitrogen or carbon. The latter is the more stable combination and an alkyl cyanide is therefore formed predominantly.

NITRILES AND ISOCYANIDES

Name	Formula	Density (20°)	Boiling Point	Solubility in 100 ml. of		
				Water	Alcohol	Ether
Acetonitrile	CH ₃ CN	.791	81.5	inf.	inf.	inf.
Propionitrile	C ₃ H ₅ CN	.780	97.1	s.	inf.	s.
Butyronitrile	C ₄ H ₇ CN	.794	118	sl.s.	inf.	inf.
Valeronitrile	C ₅ H ₉ CN	.801	141	i.	s.	s.
Isovaleronitrile	(CH ₃) ₂ CH- CH ₂ CN	.807	129	sl.s.	inf.	inf.
Isobutyronitrile	(CH ₃) ₂ CH- CN	.773	107.8	sl.s.	inf.	inf.
Methyl isocyanide	CH ₃ N:C	.746	59.6	10 (15°)	s.	inf.
Ethyl isocyanide	C ₂ H ₅ N:C	.740	79	v.s.	inf.	inf.

Alkyl isocyanides though distinct and separable from the nitriles are nevertheless convertible into nitriles by heating at 250°.



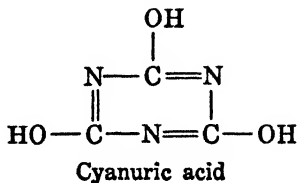
There is in this case a breaking of a carbon-nitrogen bond and the formation of a carbon-carbon bond which is more stable.

In the case of hydrocyanic acid it appears that the same type of change takes place reversibly at ordinary temperatures so that hydrocyanic acid is a mixture of HCN and HNC in which the former predominates. This is, of course, a case of tautomerism in which the change involves a shifting of hydrogen. Other atoms or groups do not shift so readily as is shown by the high temperature required for converting methyl isocyanide to the nitrile.

Cyanates and Isocyanates

Corresponding to the nitriles and isocyanides are the oxygen compounds cyanates and isocyanates. Potassium cyanide KCN may be oxidized to yield potassium cyanate which however may be represented either as $\overset{+}{\text{K}}\overset{-}{\text{N}}=\text{C}=\text{O}$ or $\overset{+}{\text{K}}\overset{-}{\text{O}}-\text{C}\equiv\text{N}$. It is a highly ionized salt and since the potassium ion is not attached either to nitrogen or oxygen the two formulas represent the same substance.

Cyanic acid itself is unstable and when exposed to ordinary room temperature polymerizes with almost explosive violence to give a substance known as *cyamelide*. This changes slowly into *cyanuric acid*, $\text{C}_3\text{H}_3\text{O}_3\text{N}_3$, which has the following structure.



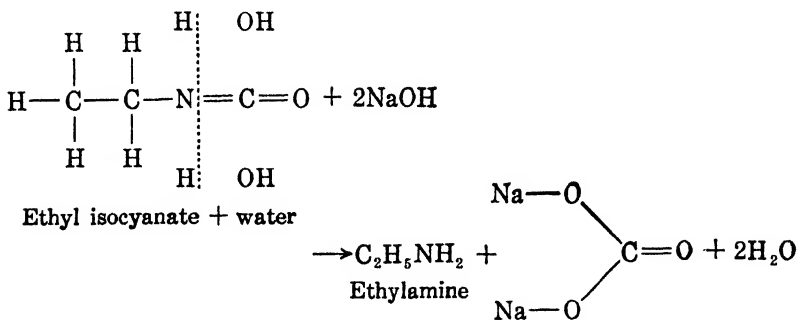
The name cyanic acid is applied to the more or less hypothetical substance with the structure $\text{H}-\text{O}-\text{C}\equiv\text{N}$. The actual substance

above which undergoes polymerization is probably a tautomeric mixture of $\text{H—O—C}\equiv\text{N}$ and H—N=C=O .

Esters of cyanic acid $\text{R—O—C}\equiv\text{N}$ have never been prepared apparently because of the readiness with which they change into cyanurates.

While isocyanic acid H—N=C=O is not known due to its tautomeric relationship with $\text{H—O—C}\equiv\text{N}$, corresponding esters are well known. One, methyl isocyanate, $\text{CH}_3\text{—N=C=O}$, has already been encountered (p. 185). These esters are formed as intermediate products in the Hoffman reaction and may be made by the oxidation of alkyl isocyanides or by the interaction of alkyl halides with silver cyanate.

Ethyl isocyanate, for example, may be considered the anhydride of ethylamine and carbonic acid, and in accordance with this relationship it is hydrolyzed in the presence of alkalis in the following manner:



If the isocyanates are available, the corresponding amines can be prepared from them by this method.

Fulminates. By the action of silver nitrate and nitric acid on alcohol there is formed by a complex series of reactions, a substance distinct from but isomeric with silver cyanate. This is known as silver fulminate.⁴ The corresponding mercury com-

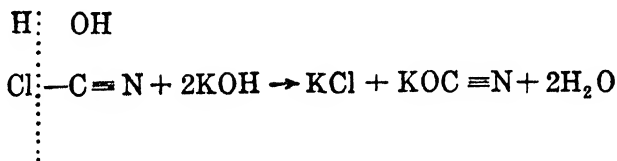
⁴ It is interesting to note that silver fulminate and silver cyanate constitute the first case of isomerism to be discovered. Liebig (p. 6) and Wöhler (p. 323) obtained the same analytical values from what they knew to be two different salts. Liebig at first questioned the accuracy of Wöhler's analysis but was later convinced.

pound, mercury fulminate, is used in priming caps as a detonator to set off other explosives. Unlike most of the explosives which are used in quantity, it explodes rather readily by percussion.

Fulminic acid of which these compounds are salts is very unstable and has never been isolated from its solution. It is very poisonous.

The structure of fulminic acid is not established with certainty. It has commonly been formulated as $\text{H}-\text{O}-\text{N}=\text{C}$ with bivalent carbon, and in keeping with this idea silver fulminate adds HCl and both atoms become attached to the carbon.

Cyanogen chloride, $\text{Cl}\cdot\text{CN}$, is a gas which can be made by the action of chlorine on hydrocyanic acid, $\text{HCN} + \text{Cl}_2 \rightarrow \text{Cl}\cdot\text{CN} + \text{HCl}$. It is the acid chloride of cyanic acid ($\text{HOC}\equiv\text{N}$) and hydrolyzes in the presence of alkalis in accordance with this relationship.

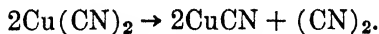


Cyanogen chloride + water

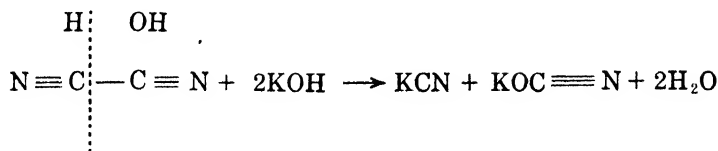
Potassium cyanate

Like cyanic acid it polymerizes; a solid substance with the molecular formula $\text{C}_3\text{N}_3\text{Cl}_3$ known as *cyanuric chloride* is formed. Cyanogen chloride was one of the poisonous gases used in World War I.

Cyanogen $(\text{CN})_2$ is a very poisonous gas which may be made by heating cupric cyanide, which is thereby converted into the cuprous salt.



It may be regarded as the mixed anhydride of hydrocyanic acid and cyanic acid (HOCN), and in alkaline solution undergoes hydrolysis accordingly. This illustrates the effectiveness of alkalis in catalyzing the splitting of carbon-carbon bonds.

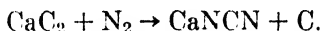


Cyanogen (+ water)

Potassium cyanate

It is hydrolyzed in the presence of *acids*, however, like other nitriles to give the ammonium salt of a dicarboxylic acid (oxalic acid). In this case the two carbon atoms remain attached and the two cyanide groups hydrolyze in the usual way.

Cyanamide is probably the amide of cyanic acid and accordingly has the structure $\text{H}_2\text{N}-\text{C}\equiv\text{N}$. Ammonia itself has feeble acid properties, and the substitution of a cyanide group for one of the hydrogen atoms should greatly increase the acid properties. Cyanacetic acid, $\text{CH}_2(\text{CN})\text{COOH}$, for example, has an ionization constant of .0037 while that of acetic acid is .000018. Cyanamide is evidently able to form salts in which both of the hydrogen atoms are replaced by a metal. *Calcium cyanamide*, $\text{CaNC}\equiv\text{N}$, an important commercial product, is used as a fertilizer, as a source of combined nitrogen for plants. It is hydrolyzed by the water in the soil forming cyanamide, $\text{H}_2\text{NC}\equiv\text{N}$, which is easily converted by further hydrolysis into urea and finally into ammonia and carbonic acid. Calcium cyanamide is made by the reaction of nitrogen obtained from the atmosphere, on calcium carbide at about 1000° .

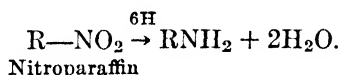


Since calcium cyanamide can be converted into ammonia and other nitrogen compounds, this constitutes one of the methods of "fixing" atmospheric nitrogen.

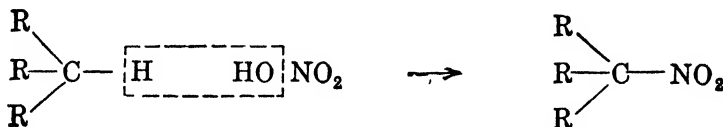
Nitro Compounds

The formation of an alkyl nitrite and a nitroparaffin by the interaction of silver nitrite and an alkyl halide has already been mentioned (p. 173). One product is an ester of nitrous acid $\text{R}-\text{O}-\text{N}=\text{O}$, in the other evidently the nitrogen is attached

directly to the carbon because its reduction results in the formation of a primary amine.



Nitro compounds have long been known to be produced by the action of dilute nitric acid at about 100° on paraffin hydrocarbons containing tertiary carbons.

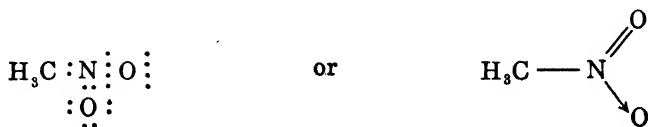


Recently, however, the high temperature vapor phase nitration of paraffin hydrocarbons has been developed (Hass) so that simple nitroparaffins are available in commercial quantities. Carbon-carbon bonds are often broken when higher hydrocarbons are nitrated and as a result simpler nitro compounds are also produced. When propane is nitrated at 420° there is obtained 1-nitropropane, 2-nitropropane, nitroethane and nitromethane.

The nitroparaffins and their derivatives are used to make pharmaceuticals, dyestuffs, insecticides, rubber chemicals, photographic developers, textile chemicals and resins. In addition to their use in synthesis, the nitroparaffins are used in polishes, cleaning compounds, vinyl resin coatings, cellulose acetate and acetobutyrate lacquers, industrial emulsions and cosmetic creams and lotions.

The nitro compounds boil about 100° higher than the corresponding nitrous acid ester, and may be regarded as anhydrides of nitric acid and hydrocarbons. They are resistant to hydrolysis compared with nitrous acid esters.

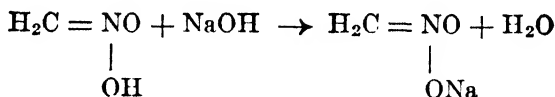
The formation of nitro compounds by the use of *silver nitrite* can probably be explained on the same basis as the formation of isocyanides using silver cyanide. (Silver and sodium sulfites also give different products with alkyl halides in a similar way, the first gives a sulfonic acid in which sulfur is attached to carbon, the second gives an ester of sulfurous acid). The structure of nitromethane may be represented as



in which there is one coordinate bond. These picture the nitro group as being unsymmetrical which is contrary to physical evidence (dipole moments). According to wave mechanics theory the nitro group is symmetrical but it is impossible to picture it by ordinary formulas inasmuch as its structure is the resultant of two unsymmetrical structures.

Nitrous acid itself probably exists in tautomeric forms, one with the ordinary structure $\text{H}-\text{O}-\text{N}=\text{O}$ the other with the resonating co-ordinate bond structure and having hydrogen attached directly to nitrogen.

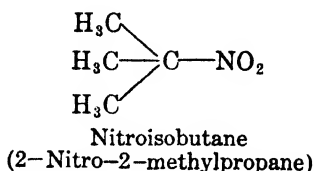
Although the nitro compounds do not change to nitrous acid esters or vice versa, an interesting tautomerism exhibits itself when the nitro compounds are placed in alkaline medium. While nitromethane appears as a neutral compound it is capable of forming stable salts by reaction with sodium hydroxide. The phenomenon is explained on the basis of the conversion of the nitromethane into an acid form, followed by its neutralization as indicated.



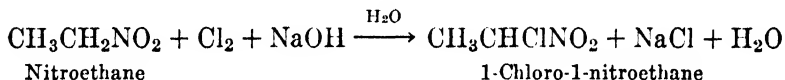
Nitromethane and various other nitro and related compounds which do not yield acid solutions and yet are capable of yielding alkali salts, are known as pseudo acids. The change to the acid form is not instantaneous and therefore we may observe a "slow neutralization." When a strong acid is added to a solution of a sodium salt of a pseudo acid the pseudo acid tends to become free and may crystallize from the solution (depending on its solubility). Such a free pseudo acid on standing reverts slowly to the neutral form. In neutral or acid solutions the equilibrium between the two forms is much in favor of the neutral form, but equilibrium is attained only slowly.

That the potential acid properties of the nitro compounds is due to a shift of hydrogen from the neighboring carbon atom,

is shown by the fact that when this carbon atom holds no hydrogen no potential acid properties exist. This is true in the case of the nitrobutane represented below.

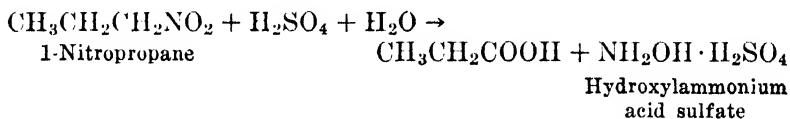


A number of reactions of both theoretical and technical importance are made possible because of the tautomerism shown by nitroparaffins. Chloronitroparaffins, in which the chlorine and nitro radicals are attached to the same carbon atom, are formed by chlorinating the sodium salts of the nitroparaffins.



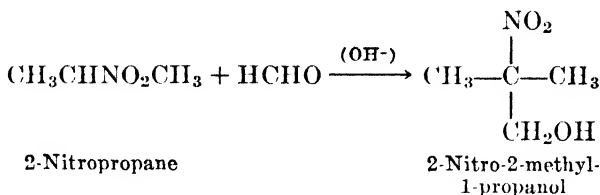
Chloropicrin, CCl_3NO_2 , an effective larvicide and lachrymator, is prepared from nitromethane by a similar reaction.

When primary nitroparaffins are treated with mineral acids the following type of reaction takes place:

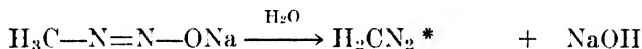
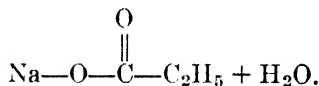
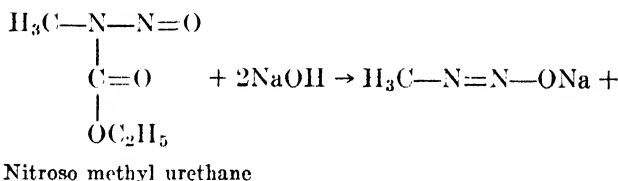


Not only does this reaction give a means of producing fatty acids but it also produces very reactive by-products, hydroxyl ammonium salts, which are used in the synthesis of dyestuffs, pharmaceuticals, resins, flotation agents and many other organic chemicals.

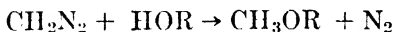
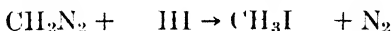
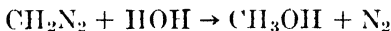
Nitroparaffins react with aldehydes in the presence of a basic catalyst in a reaction similar to an aldol condensation (p. 108). Nitrohydroxy compounds are produced by this reaction.



Diazo Paraffins. The most important diazo paraffin is diazomethane, CH_2N_2 . It is best made by a rather complicated reaction involving nitroso methyl urethane, a compound of a type which we have not yet mentioned (see p. 3225). The course of the reactions is indicated below:



Diazomethane is of interest and importance because it reacts rather readily with water, alcohols, acids, amines and various other compounds to yield nitrogen gas as one product and a methyl derivative as the other product. It is therefore used as a *methylating agent*. A few examples of its reactions are cited below. It is a yellow gas which is odorless but poisonous.



PROBLEMS

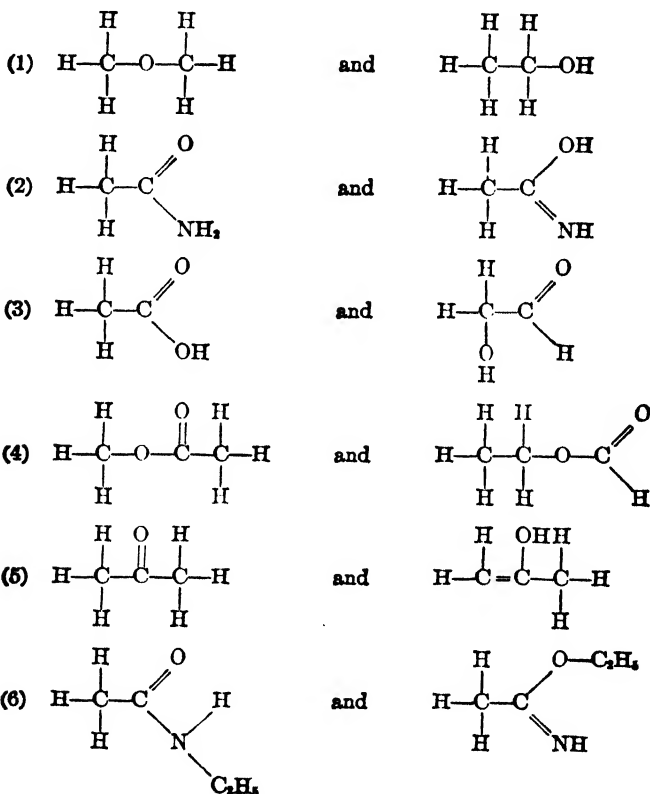
1. Compare the molecular formulas of ammonium cyanate and urea (p. 181). How could you hope to distinguish the two substances?

* There is conflicting evidence regarding the structure of diazomethane. The strongest evidence indicates that it has a colinear structure such as $\text{H}_2\text{C}=\text{N}^+=\text{N}^-$ rather than a three membered ring. Resonance is probably also involved.

2. Work out the equations for the reactions that would be involved in the following transformations: (a) methyl bromide \rightarrow acetic acid, (b) methyl alcohol \rightarrow ethyl alcohol, (c) ethyl amine \rightarrow propionitrile.

3. How could ethyl ammonium formate, the hydrolysis product of ethyl isocyanide, be distinguished by a simple laboratory test from ammonium propionate, the hydrolysis product of propionitrile?

4. Would you expect the following isomers to be in tautomeric equilibrium? What are the reasons?



5. In what way can a Grignard reaction be used to add one carbon atom to a chain?

6. If 5 grams of acetonitrile is in one case reduced, and in another case the same amount of acetonitrile is hydrolyzed and the ammonia recovered, how will the neutralizing power of the amine and the ammonia produced by the different operations compare?

7. How could isobutyric acid be prepared starting with acetic acid, making use of pyrolysis of a calcium salt and reduction, in addition to the reactions discussed in this chapter?

8. Silver sulfite and potassium sulfite yield isomeric sulfur containing compounds on being heated with methyl iodide. What possible formulas could be ascribed to the compounds?

9. Two silver nitrites are known, α and β . Write the possible electronic structures and indicate how you might expect them to react with alkyl halides. (It appears that the experiment has never been tried.)

10. What objection can be raised to the idea of using diazomethane as a reagent for hydroxyl groups, and using the nitrogen evolved as a measure of the extent of the reaction?

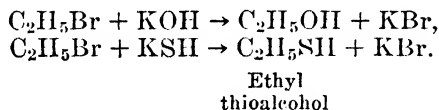
11. Suppose that a substance with the structure $\text{H}-\text{N}=\text{C}$ undergoes hydrolysis like the other isocyanides, what substances will result?

CHAPTER XIII

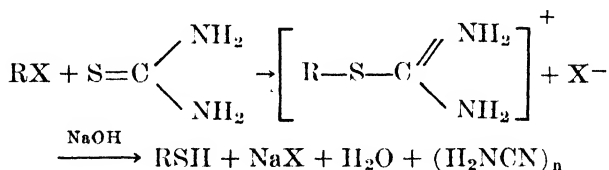
SULFUR COMPOUNDS

Sulfur and oxygen belong to the same family and it is not surprising therefore that many organic compounds are known in which sulfur plays the part taken by oxygen in the commoner compounds. The differences between sulfur and oxygen compounds can usually be attributed to the fact that the sulfur kernel has one more electron layer than the oxygen kernel. Sulfur, therefore, has a smaller effective nuclear charge and consequently a greater electron mobility.

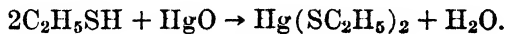
Thioalcohols can be prepared by the action of potassium hydrogen sulfide on alkyl halides. This is analogous to the treatment of an alkyl halide with dilute alkali.



The thioalcohols can also be prepared by the reaction between either alkyl halides or alkyl sulfates and thiourea.

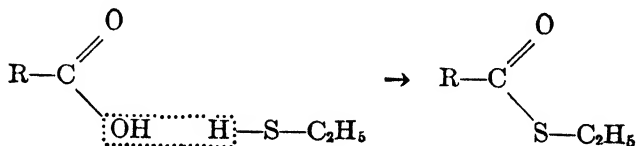


Thioalcohols were early given the name *mercaptans* because they easily form crystalline mercury salts. The acid properties of the mercaptans or thioalcohols are stronger than the alcohols just as H_2S is more highly ionized than H_2O . The formation of a mercury salt (*mercaptide*) takes place by the action of the thioalcohol on mercuric oxide.



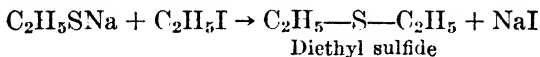
Mercaptans are present in petroleum distillate from which hundreds of tons daily could be obtained if there were a sufficient demand. The most characteristic feature of mercaptans is their onion or garlic-like odor. It has been estimated that one part in fifty billion of ethyl mercaptan in air may be detected by odor. Because of this property both ethyl and pentyl mercaptan (Pentalarm) are used as warning agents in odorless fuel gases. Butyl mercaptan is present in the defensive secretion of the skunk.

Formation of Esters. It is interesting to note that when a thioalcohol is treated with an acid to form an ester, the reaction takes the following course.



The acid furnishes the hydroxyl group and the thioalcohol furnishes the hydrogen atom. Hydrogen sulfide might be eliminated and an ordinary ester formed, but this is not the case. The product is called a **thioester**. The course of this reaction is in line with other evidence, that when acetic acid and ethyl alcohol react, the acetic acid furnishes the hydroxyl group while the alcohol furnishes the hydrogen.

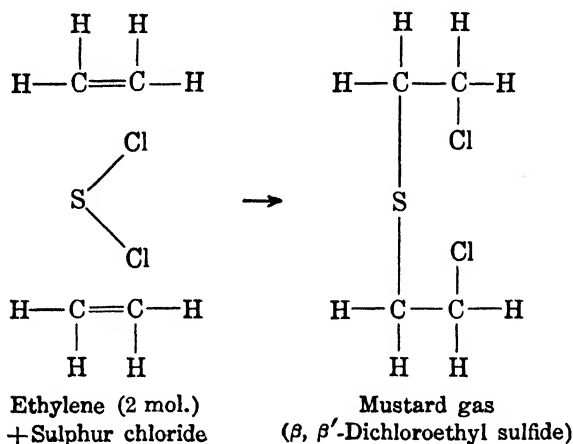
Thioethers (sulfides) can be prepared in a manner analogous to the formation of ordinary ethers—



The thioethers may be regarded as the di-esters of hydro-sulfuric acid, H_2S . They are, however, quite stable and are not readily hydrolyzed by alkalis. Ordinary ethers are also stable toward hydrolysis and are unaffected by alkalis. This is correlated with the fact that they do not produce any distinctly acid substance on hydrolysis. The sulfides have disagreeable odors but they are not as objectionable as those of the mercaptans.

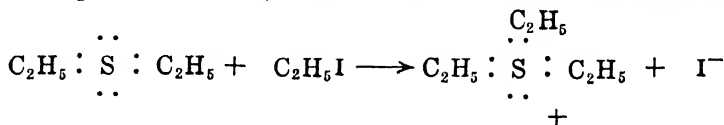
A derivative of diethyl sulfide is known as "mustard gas" and was extensively used in chemical warfare. It is a liquid,

boiling at 216° , and may be made by the action of sulfur chloride on ethylene.



Chemically it is called β, β' -dichloroethyl sulfide. The mark (') is used to indicate that the second chlorine atom is substituted in the second ethyl group.

The formation of ammonium and oxonium salts has already been discussed. In a similar manner diethyl sulfide, for example, forms an addition product with ethyl iodide which is termed a *sulfonium* salt.



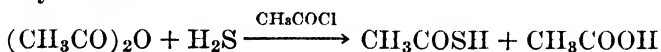
Triethyl sulfonium iodide

Triethyl sulfonium iodide may be treated with moist silver oxide (silver hydroxide) to form triethyl sulfonium hydroxide which is a strong base analogous in structure to the quaternary ammonium bases (p. 191).

Thioaldehydes and thioketones are often difficult to prepare in the monomolecular state because they polymerize very readily. They are blue in color and have very disagreeable odors. The $\text{C}=\text{S}$ group shows more pronounced unsaturated properties than the carbonyl group.

Thioacids, in which the SH group takes the place of the hydroxyl group in carboxylic acids, can be prepared in good yields

by passing hydrogen sulfide into a mixture of acetic anhydride and acetyl chloride.



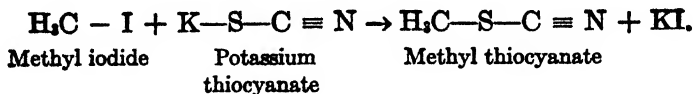
Thioacetic acid, CH_3COSH , as might be expected is considerably stronger than acetic acid. It is a liquid boiling at 93° . Other thioacids also have lower boiling points than the corresponding oxygen acids. Reference to the table will show that the lower molecular weight thioalcohols and thioacids in general have lower boiling points than the corresponding oxygen compounds but that the thioethers boil at considerably higher temperatures than the ordinary ethers. Hydrogen sulfide has, of course, a much lower boiling point than water.

BOILING POINTS OF OXYGEN AND SULFUR COMPOUNDS

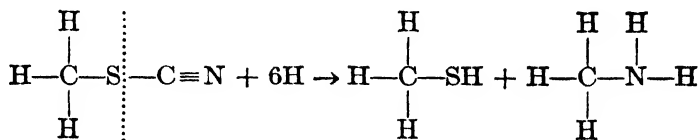
<i>Ethers</i>							
	$(\text{CH}_3)_2\text{O}$	$-\text{23.6}^\circ$		$(\text{CH}_3)_2\text{S}$	37.5°
	$(\text{C}_2\text{H}_5)_2\text{O}$	34.5°		$(\text{C}_2\text{H}_5)_2\text{S}$	$92.^\circ$
<i>(n)</i>	$(\text{C}_3\text{H}_7)_2\text{O}$	$91.^\circ$	<i>(n)</i>	$(\text{C}_3\text{H}_7)_2\text{S}$	141.2°
<i>(n)</i>	$(\text{C}_4\text{H}_9)_2\text{O}$	142.4°	<i>(n)</i>	$(\text{C}_4\text{H}_9)_2\text{S}$	182°
<i>Alcohols</i>							
	CH_3OH	64.5°		CH_3SH	$6.^\circ$
	$\text{C}_2\text{H}_5\text{OH}$	78.4°		$\text{C}_2\text{H}_5\text{SH}$	34.7°
<i>(n)</i>	$\text{C}_3\text{H}_7\text{OH}$	97.4°	<i>(n)</i>	$\text{C}_3\text{H}_7\text{SH}$	$68.^\circ$
<i>(n)</i>	$\text{C}_4\text{H}_9\text{OH}$	117.9°	<i>(n)</i>	$\text{C}_4\text{H}_9\text{SH}$	$98.^\circ$
<i>Acids</i>							
	CH_3COOH	118°		CH_3COSH	93°
<i>(n)</i>	$\text{C}_3\text{H}_7\text{COOH}$	163.5°	<i>(n)</i>	$\text{C}_3\text{H}_7\text{COSH}$	130°

The acid corresponding to acetic acid in which all of the oxygen is replaced by sulfur CH_3CSSH is called *methyl dithionic acid*. Derivatives of the thioacids such as "anhydrides," etc., are also known but are not of sufficient importance to be discussed individually.

Thiocyanates and Isothiocyanates. Although alkyl cyanates are not known, the corresponding alkyl *thiocyanates* are known; also the alkyl *isothiocyanates*. Methyl thiocyanate can be made by the action of potassium thiocyanate on methyl iodide.

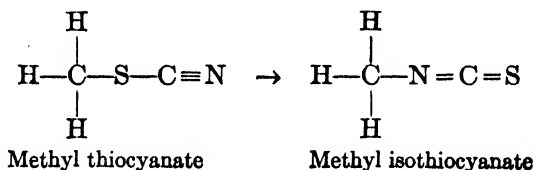


It is known to have the structure given because on reduction it yields methyl thioalcohol and methylamine.



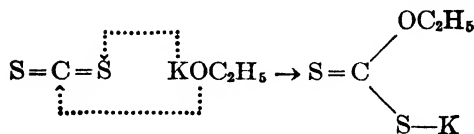
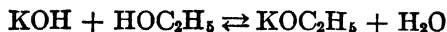
Lauryl thiocyanate, $\text{C}_{12}\text{H}_{25}\text{SCN}$, and butyl carbitol thiocyanate, $\text{C}_4\text{H}_9\text{OCH}_2\text{CH}_2\text{OCH}_2\text{CH}_2\text{SCN}$ (Lethane), are important agricultural insecticides.

By prolonged heating the alkyl thiocyanates may be converted into the corresponding isothiocyanates.



This change involves the breaking of a rather stable bond and does not take place easily. The alkyl isothiocyanates are frequently called the *mustard oils*. The name gets its origin from the fact that the active ingredient of mustard is *allyl isothiocyanate*, $\text{CH}_2=\text{CHCH}_2\text{NCS}$. ($\text{CH}_2=\text{CHCH}_2\text{OH}$ is allyl alcohol.)

Carbon disulfide, CS_2 , is the sulfur analog of carbon dioxide, to which it shows some similarities. It can be made by direct union of the two elements at high temperature, just as carbon dioxide is formed by combustion of carbon. There are several possible acids similar in structure to carbonic acid, with part or all of the oxygen replaced by sulfur, but they are all unstable and most of them have not been prepared. The most important compounds derived from acids of this type are the *xanthates*. It was noted that carbon dioxide adds potassium ethylate to form potassium ethyl carbonate (p. 174). In a similar way carbon disulfide adds potassium ethylate, when put into an alcoholic solution of potassium hydroxide.



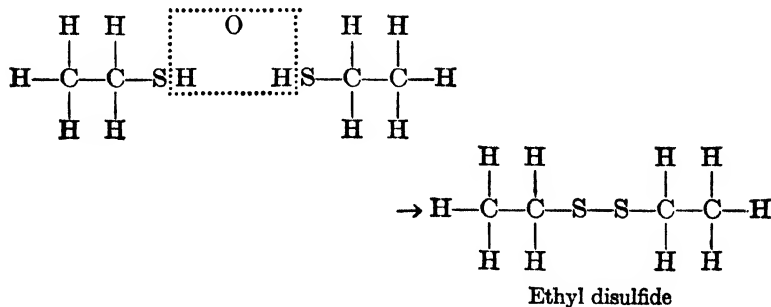
Potassium ethyl xanthate

The substance formed crystallizes in yellow needles and is known as *potassium xanthate* (from Greek meaning yellow). Sodium ethyl xanthate (also called ethyl xanthate) is used extensively as an agent in ore flotation. About 10,000,000 pounds of xanthates, including the butyl and isoamyl esters, are produced yearly for ore flotation in the United States.

A reaction similar to that pictured above has an important technical application in the manufacture of rayon, from cellulose.

Other Sulfur Compounds. The compounds so far discussed are analogous to corresponding oxygen compounds, and in general may be made by similar methods. Atomic structure studies have emphasized the fact that the elements of the first period of the periodic table show distinct differences from the elements in the succeeding periods. Thus sulfur which is in the second period shows definite contrasts to oxygen which is in the first period. This is obvious when it is noted that there are no oxygen compounds analogous to sulfuric and sulfurous acids.

When thioalcohols are oxidized, substances are formed which are unlike any that can be obtained from ordinary alcohols. The first oxidation products formed are the *disulfides* in which two sulfur atoms are attached to each other.

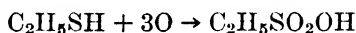


This joining of sulfur atoms is one of the ways in which sulfur shows a contrast to oxygen. Diethyl peroxide, $\text{C}_2\text{H}_5\text{—O—O—C}_2\text{H}_5$, is in fact known but it cannot be made by oxidation of ethyl alcohol, and does not closely resemble the disulfides.

In protein molecules sulfur atoms are frequently linked together as in the disulfides. Allyl disulfide, $(\text{CH}_2=\text{CHCH}_2)_2\text{S}_2$, is the chief constituent of oil of garlic.

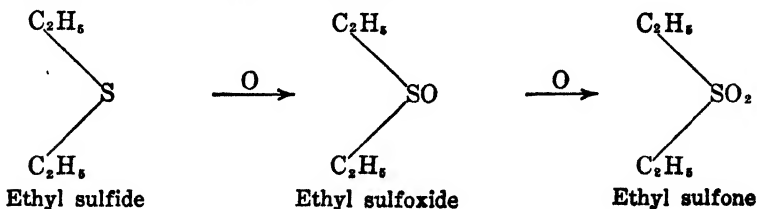
Sulfur itself in the vapor state exists as complex molecules with as high as eight sulfur atoms to the molecule. This shows the tendency which sulfur atoms have of joining together probably in rings. Ammonium sulfide on standing in solution loses ammonia and becomes "yellow ammonium sulfide" which is a mixture of polysulfides represented by the formula, $(\text{NH}_4)_2\text{S}_x$. Certain important dyes to be mentioned later have a large amount of sulfur in combination probably in a similar manner.

When thioalcohols are oxidized more vigorously (with nitric acid), *sulfonic acids* are formed, according to the following—



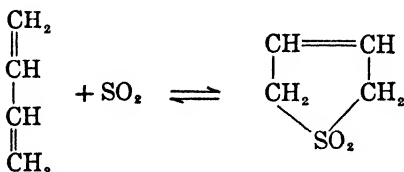
These substances have strong acid properties because one of the ionizable hydrogen atoms is in the same combination as in sulfuric acid. They are unlike the alkyl sulfuric acids (esters) in that they have one oxygen atom less, and do not undergo hydrolysis. They have the same relationship to sulfuric acid as the nitro compounds do to nitric acid, and are not esters. The fact that sulfur is attached to carbon is shown by its attachment to carbon in the original thioalcohol and by the fact that the substances do not behave like esters. Certain hydrocarbons form sulfonic acids directly by treatment with sulfuric acid.

The oxidation of diethyl sulfide with nitric acid produces first *ethyl sulfoxide* (a sulfurous acid derivative) and finally *ethyl sulfone* (a sulfuric acid derivative).



The sulfones are more nearly analogous to the nitro compounds because there are no hydroxyl groups in their structure.

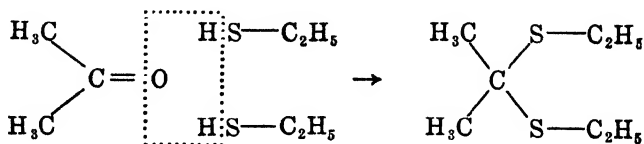
Cyclic sulfones can be made by the 1,4-addition of sulfur dioxide to diolefins.



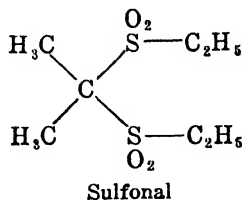
While the structures of sulfuric and sulfurous acid and their derivatives have traditionally been represented as though double bonds existed between sulfur and oxygen, evidence (p. 618) indicates that coordinate bonds are present and that the sulfoxide and sulfone represented above should be represented electronically thus:



Sulfonal is one of a series of important sleep-producing drugs (soporifics). When acetone is treated with ethyl thioalcohol in the presence of hydrochloric acid a reaction takes place which is similar to the formation of an acetal from an alcohol and an aldehyde (p. 105).



Oxidation of the resulting di-thioether produces a di-sulfone which is *sulfonal*—



Trional has an ethyl group in the place of one of the methyl groups and thus has three ethyl groups in its structure. *Tetronal* has four ethyl groups. The slight change in constitution involved in the substitution of an ethyl group for a methyl modifies very appreciably the physiological action of the drugs though they act similarly.

PROBLEMS

1. How would the extent of hydrolysis of sodium ethyl mercaptide compare with that of sodium ethylate under like conditions?

2. Into what are disulfides converted when they act as oxidizing agents?

3. How would you explain the fact that there are two series of esters, alkyl thiocyanates and alkyl isothiocyanates, but only one corresponding acid, namely, thiocyanic acid?

4. How many dichloro ethyl sulfides would be possible? Write the structural formulas for β,β -dichloro ethyl sulfide, and α,α' -dichloro ethyl sulfide.

5. How would you expect methyl magnesium bromide to react with ethyl mercaptan?

6. What ketones would be used in the making of trional and tetronal? According to the formula given would "sulfonal" have acid properties?

7. Allyl alcohol has somewhat stronger acidic properties than the ordinary alcohols. With what other fact can this be correlated? Is allyl alcohol the enol form of an aldehyde?

8. Write the electronic formula for an isomer of ethyl sulfonic acid, in which only one coordinate valence appears. How would the properties of this compound compare with those of ethyl sulfonic acid?

CHAPTER XIV

POLYFUNCTIONAL ALIPHATIC COMPOUNDS

So far in our study we have been concerned almost exclusively with compounds which may be considered as relatively simple derivatives of the paraffin hydrocarbons. Many of the more important compounds which we will wish to study are more complex, in that they have in their structure different kinds of groups, or several groups of the same kind. Glycerol is an example of a compound which is not a simple alcohol, but contains three hydroxyl groups in its structure, and is hence an alcohol three times over. We shall encounter compounds which have two or more carboxyl groups, two or more amino groups, two or more ketone groups, etc., in the molecule. In addition to these there are the "mixed" compounds which contain two or more different kinds of groups, such as alcohol and carboxyl, amino and carboxyl, or aldehyde and alcohol, etc.

The principal types of derivatives which have been studied are: those containing double or triple bonded carbon atoms, the alcohols, ethers, aldehydes, ketones, acids, salts, and anhydrides, esters, amides, nitriles, amines. This list omits several types of compounds including all of the sulfur compounds. A compound may have in its structure any two of the groups characteristic of the above compounds. There are sixty-six different combinations of these groups taken two at a time, and corresponding to these there are sixty-six different *types* of compounds, of which in some cases a number of representatives might be mentioned. There are, in addition to these, many examples of compounds which contain more than two of these groups at the same time, or may contain several of the same kind of group, and in addition other groups as well. All of such compounds may be classed together as "polyfunctional" because they have more than one reactive group.

It is obviously impossible to study all of these numerous types

of compounds in detail, but fortunately we can learn much about them without a detailed study. There are some general principles which make it possible to know the general properties of such compounds without individual study, provided their formulas have been established.

An important principle to bear in mind is that each individual group has its individual characteristics and reactions, and if present in the molecule, will exhibit these characteristics. Thus an alcohol remains an alcohol, whether the compound containing the alcohol group is at the same time an acid, an aldehyde, an amine, a salt, an ether, or any other sort of compound. An acid remains an acid regardless of whether there are groups typical of other compounds in the same molecule. Following this principle, it may be pointed out that if two groups are present in the same molecule which in general have the ability to react with one another under certain conditions, they will react *within the molecule* unless there is some reason why the reaction cannot take place. Some other reaction may take place first in some cases and thus eliminate the possibility of intramolecular reaction.

A second fact to bear in mind is that although each group retains its fundamental characteristics, the properties of the group will in general be *modified* by the presence of neighboring groups. Thus while an acid will retain its acid properties when various other groups are in the molecule, it may become a very weak acid or a very strong acid, depending on the character of the other groups present. We have already noted cases of this kind. Since we shall be dealing frequently with compounds which have more than one of the characteristic groups, the modification of properties resulting from the influence of neighboring groups will be an important factor.

Though the general properties of compounds are determined by the particular groups in their structure, it is not possible to picture with a high degree of accuracy the behavior of a compound under different conditions from a consideration of the groups present in its structure. We shall want to study certain compounds in more detail, and in order to do this many different types of compounds must be left out of extended consideration. The compounds which we shall study more intensively will be

those that are important from some particular standpoint. In the remaining chapters of this book *substances will in general be left out of consideration unless they are (1) theoretically important or interesting, (2) biologically important, or (3) important from the technical or manufacturing standpoint.*

PROBLEMS

1. Construct formulas which represent compounds of the following types: (a) amine-alcohol, (b) ester-acid, (c) ketone-acid, (d) salt-ketone, (e) nitrile-acid, (f) ether-alcohol, (g) ester-ether, (h) aldehyde-alcohol, (i) di-amine, (j) di-acid, (k) di-alcohol acid, (l) salt-acid-alcohol-ether.

2. Would it be possible to prepare a compound which is at the same time an acid and a base? If such a compound should form momentarily, what would result? Would the results be the same if one should prepare an alcohol-acid?

3. What types of mixed compounds are (a) methyl formate, (b) chloroacetic acid, (c) chloral, (d) "mustard gas," (e) sodium ethyl xanthate?

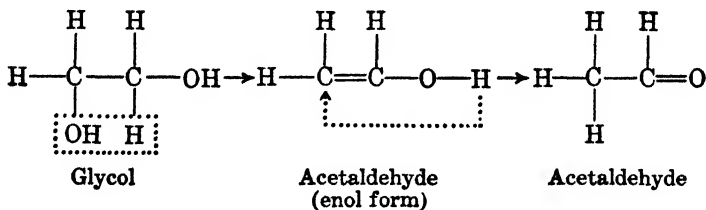
CHAPTER XV

POLYALCOHOLS AND THEIR DERIVATIVES

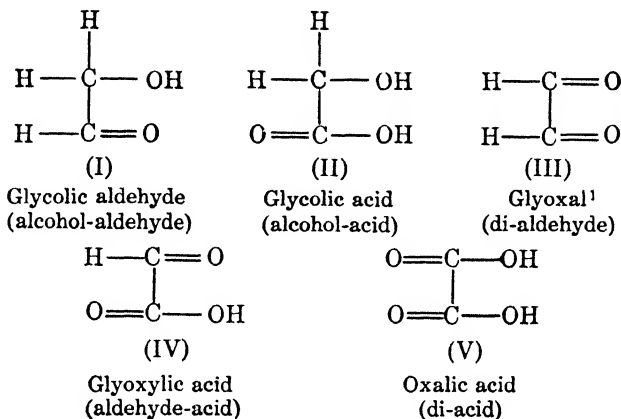
When ethylene gas is bubbled through liquid bromine *ethylene dibromide* is formed. This can be hydrolyzed in dilute alkaline solution to form ethylene glycol $\text{CH}_2\text{OHCH}_2\text{OH}$, which is an alcohol twice over. The same compound is formed usually in small amounts by the oxidation of ethylene (p. 51). It is a sweet tasting (Gr. *glykys*, sweet) viscous liquid boiling at 197° , soluble in water but like other compounds containing more than one alcoholic hydroxyl group not very soluble in ether.

Until a relatively few years ago this compound was a comparative rarity of no importance or use. Today as a result of cheap methods of manufacture with ethylene as the starting material, it is an important product not only because of its direct uses but also because of the importance of various derivatives to be discussed shortly. Its low molecular weight, low volatility and lack of solvent action on rubber and automobile finishes make it an excellent antifreeze compound for radiators, which constitutes its major direct use. Because of its stability, high boiling point and low freezing point, it is also used as a coolant in liquid cooled airplane engines.

It is the first member of a series of dihydroxy alcohols, known as *glycols*, and its general chemical characteristics can be predicted on the basis of its structure. Being a dialcohol it can react with acetyl chloride, acetic anhydride or acetic acid to form first a mono-ester then a di-ester. It reacts with strongly positive metals such as sodium to form first a mono-sodium salt and then at higher temperature the di-sodium salt. Strong dehydration yields acetaldehyde presumably according to the following:



The oxidation of glycol takes place in a manner which might be expected of a di-primary alcohol. Various products are formed in different proportions depending on the agent used, its concentration, the temperature, and other conditions. The formulas given below represent all the intermediate products.



Glycolic acid and oxalic acid are perhaps the most important of these oxidation products and will be mentioned again later. Of these substances, the first, third and fourth contain aldehyde groups, and show the properties of aldehydes, as for instance in their extreme case of oxidation. The first and second substances show all the characteristics of primary alcohols, and the three carboxylic acids show distinct acid properties; each is stronger than acetic acid.

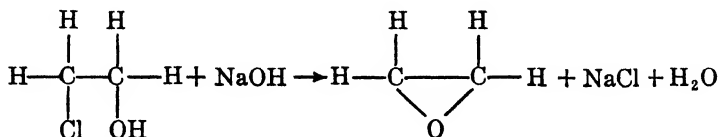
Glycol owes its importance not to any of the derivatives so far mentioned but to a number of those which though not made directly from glycol are closely related to it.

¹ Dimethyl glyoxime is the di-oxime of dimethyl glyoxal and has the formula

$$\begin{array}{c} \text{NOH} \quad \text{NOH} \\ || \quad \quad || \\ \text{CH}_3-\text{C}-\text{C}-\text{CH}_3 \end{array}$$

It is an acid substance and is used to precipitate nickel in qualitative and quantitative analysis. Dimethyl glyoxal (diacetyl) itself is the simplest diketone and occurs in various essential oils (p. 389) and in butter. The fragrance of the latter is largely due to this compound.

Ethylene chlorhydrin, $\text{CH}_2\text{OHCH}_2\text{Cl}$, is important because it is the starting point for the production of glycol, chlorex (p. 92), divinyl ether and acrylate resins (p. 285). It is prepared by the interaction of ethylene and hypochlorous acid (chlorine water) (p. 53). While it can be used for the synthesis of a number of different types of organic compounds, its principal application is in the production of ethylene oxide which is made from it by the action of very concentrated alkali.



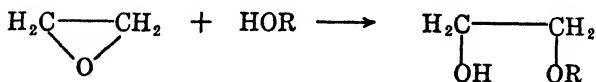
Ethylene chlorhydrin

Ethylene oxide

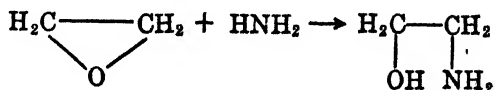
Ethylene oxide is more commonly prepared by the direct high temperature oxidation of ethylene with oxygen or air over a silver catalyst (p. 54). It may be regarded as an inner ether of glycol, and is an example of a "ring" compound. As we shall note later cyclic compounds with as few as three atoms in the ring are unstable due to a strained condition in the molecule. The important reactions of ethylene oxide involve the breaking of this ring which takes place by reaction with water, alcohols, ammonia and amines.

Ethylene oxide is readily hydrolyzed to glycol by dilute acid and this constitutes a commercial method for the synthesis of this compound.

With alcohols in the presence of an acid catalyst ethylene oxide reacts in an analogous fashion to yield an ether-alcohol.

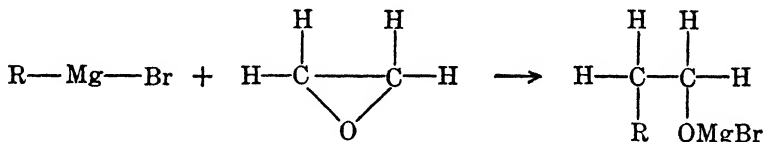


With ammonia the first step involves a similar break producing an alcohol amine, *ethanolamine*.



This compound itself can react with a further amount of ethylene oxide yielding *di-* and finally *triethanolamine*. The compounds in reacting with acids behave like ammonia. However, they have high boiling points, hence they can be used to absorb carbon dioxide from inert gases and to give it up upon heating. They are used principally for the production of soaps which are practically neutral and hence inert chemically. These soaps are also soluble in gasoline (dry cleaning) as well as water and can be used as emulsifying agents in a variety of ways.

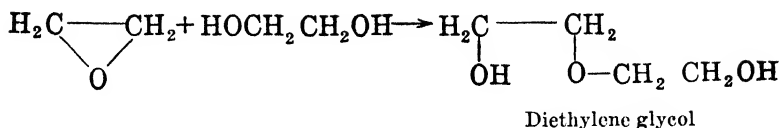
Ethylene oxide also reacts with Grignard reagents to form addition products.



These are easily convertible into primary alcohols which have two more carbon atoms than the Grignard reagent used. This constitutes an important method for the synthesis of higher alcohols from lower, *e.g.*, *n*-hexanol from *n*-butanol.

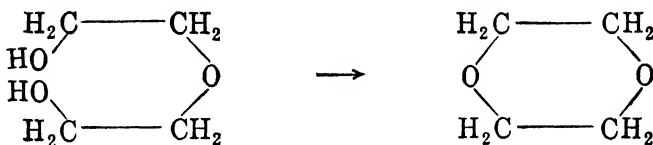
The most important of the reactions of ethylene oxide is that with alcohols, for the products formed are very important solvents used in the production of pyroxylin and related lacquers (also rayon) to be discussed later. The student may be reminded at this point that so-called "nitrocellulose" will dissolve in neither ether nor alcohol, but dissolves readily in a mixture of the two solvents to form "collodion." There is formed by interaction of ethyl alcohol and ethylene oxide a compound which is obviously both an ether and an alcohol. As might be expected it dissolves pyroxylin alone. It is sold under the name **cellosolve**. With butyl alcohol **butyl cellosolve** is formed which has similar solvent powers but is less volatile. **Methyl cellosolve** is more volatile.

Ethylene oxide reacts with glycol to produce **diethylene glycol**.



This compound is itself a solvent for "nitrocellulose" and resins used in the lacquer industry and is used in the textile industries, and as a humidifier in tobacco. The ethers of glycol (cellosolves) can also react with ethylene oxide to produce ethers of diethylene glycol which are sold under the name of **carbitols**. These solvents, in spite of their relatively high molecular weights, are miscible with water yet are also good solvents for oils and other organic compounds.

Under dehydration using an acid catalyst diethylene glycol yields a cyclic (sí'klik) diether **dioxan**.



This is an unusual solvent because it is miscible with water in all proportions and yet contains no hydroxyl group and hence is inert. Its water solubility may be correlated with the fact of its high percentage of oxygen (nearly 40 per cent). It not only dissolves many water soluble substances but also fats and oils, even mineral oils, also waxes, resins and cellulose derivatives. Because of the properties mentioned it is an important solvent in chemical laboratories and elsewhere. Dioxane, however, is highly toxic and forms explosive peroxides readily, both of these properties restrict its use as a solvent. It has been used to some extent for cryoscopic molecular weight determinations. Its "constant" is 4.7 and its freezing point is at a convenient temperature, 11.67°. With sulfuric acid it forms a stable oxonium salt, m.p. 101°.

Homologous glycols. Several homologs of ethylene glycol are listed in the table (p. 243). Of these **propylene glycol** should

be mentioned because it is of sufficient importance as a solvent to be on the market in tank car lots. It is formed from propylene oxide in a manner analogous to that of its lower homolog.

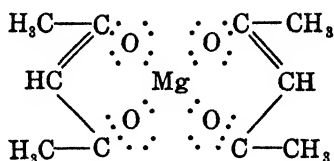
It is obvious that there is a great variety of solvents derived from glycols from which the lacquer, plastic or rayon manufacturers may choose. Solvent properties of any desirable type, any degree of volatility and other desirable properties may be combined in one compound, though a mixture of solvents is usually used, as will be indicated later.

Glycol dinitrate, $\text{CH}_2\text{NO}_3\text{CH}_2\text{NO}_3$, is a derivative of glycol of quite different types, which is used extensively as an explosive. It is much like "nitroglycerin" (p. 240) to which it is practically equivalent in effectiveness. It has at least one distinct advantage in that it remains liquid (and hence relatively insensitive to shock) at low temperature (-22°) while "nitroglycerin" freezes at $+13^\circ$. It is mixed with "nitroglycerin" to lower its freezing point.

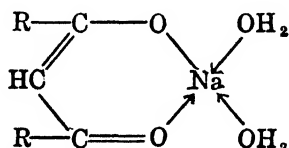
Chelate Compounds. *Acetyl acetone*, $\text{H}_3\text{C}-\text{CO}-\text{CH}_2-\text{CO}-\text{CH}_3$, is a diketone which may be considered as a derivative (oxidation product) of one of the glycols. It, in common with other β diketones and certain other compounds, exhibits valence phenomena which make it very interesting from the theoretical standpoint. The behavior is also the basis for practical applications to problems of mordant dyeing.

Acetyl acetone evidently exists in an enol form and forms a sodium salt with the structure $\text{H}_3\text{C}-\text{CONa}=\text{CH}-\text{CO}-\text{CH}_3$, which exhibits the characteristics of the sodium salt of an enol. The corresponding derivatives (of which a large number is known) in which *other metals* such as Be, Mg, Al, etc., take the place of sodium exhibit remarkable peculiarities; they have low melting points, are volatile, slightly soluble and non-conducting in water (with which they do not react!) and are soluble in organic solvents, even hydrocarbons.

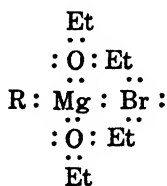
As previously mentioned (see p. 130) metals (except those of high atomic number p. 208) do not remain attached to oxygen in salts because their electron shells are far from complete and the structures formed are therefore unstable. In the case of the magnesium derivatives of acetyl acetone, however, the situation is entirely changed in that there is a means whereby the magnesium octet is made complete. The structure of the magnesium compound is represented below (for clarity only the electrons in the magnesium and oxygen shells are indicated).



The magnesium has a complete octet by virtue of the two coordinate valences in which oxygen has acted as "donor," hence it has no tendency to free itself from all these electrons and break away as a magnesium ion. The structure indicated is one of a large number of *chelate* (Greek, crab's claw) compounds which have been investigated and there can be no reasonable doubt as to the correctness of the structure. Even sodium salts of enols of diketones may become chelate by hydration. Thus we have the anomaly of a substance losing its water solubility and gaining hydrocarbon solubility *by hydration*. The structure formed is represented as follows, in which sodium has a complete octet.



The Grignard reagents are almost always formed in ether solution and attempts to purify them may result in compounds in which there are two molecules of ether $\text{R}-\text{Mg.X.2}(\text{C}_2\text{H}_5)_2\text{O}$. While this is not a chelate compound (no rings being present) it is supposed that the reason for the association with ether is the completion by coordinate links of the electron shell of the magnesium by the oxygen of the ether. The reversible formation of the complex represented below serves to explain why Grignard reagents appear to be only slightly ionized.



Glycerol $\text{CH}_2\text{OHCHOHCH}_2\text{OH}$ or glycerine as it is commonly called was, before the advent of glycol and propylene glycol, the only poly-alcohol of great importance. Its importance is based upon the facts that as a by-product of soap manufacture it is readily available in large quantities at a low cost and that

it has a great many uses (some 1,583 different uses have been listed).

In addition to the formation by hydrolysis of fats, glycerol is produced in small amounts by the fermentation of sugar by yeast, and under certain conditions the amount produced is greatly increased.

Recently, in spite of the cheapness of glycerol, technical methods of synthesis have been developed. Synthetic glycerol can thus compete with natural glycerol and keep its price low. Propylene is the starting material and is converted into allyl chloride by direct chlorination (see p. 55) at high temperature. Allyl chloride is then converted into glycerol chlorohydrin from which glycerol is obtained by alkaline hydrolysis. Synthetic glycerol has also been produced by the destructive hydrogenation of sugar.

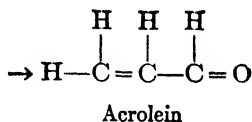
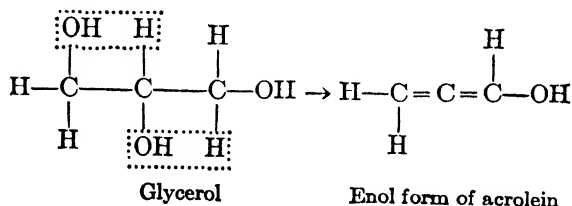
Glycerol like glycol is a viscous, hygroscopic liquid with a sweet taste. It is soluble in water in all proportions but is practically insoluble in ether. When very pure it boils at 290° without decomposition, but ordinarily the distillation is carried on under diminished pressure to avoid the effects of so high a temperature. The four principal uses of glycerol are in the production of glyptal (alkyd) resins (p. 380) and "nitroglycerin" (p. 270), as a plasticizer for cellophane (p. 381) and as a humidifier for tobacco. About 200,000,000 pounds of glycerol are used in the United States each year at a normal cost of about $12\frac{1}{2}$ cents per pound.

Glycerol is chemically like glycol. It forms esters in which one, two or three hydroxyl groups are involved. The acetic esters are known respectively as *mono*, *di*- and *triacetin* and have been used technically as solvents. The nitric acid tri-ester is commonly known as "nitroglycerin." The oxidation of glycerol like that of glycol produces various products as might be anticipated from its structure. Some of these oxidation products will be mentioned later.

The accumulation of the hydroxyl groups in the structure increases the acidic property. In common with other poly-alcohols it is not only able to react with alkali metals, etc., but also to dissolve various metallic oxides with the formation of alco-

holates. Copper hydroxide, for example, is dissolved by glycerol and other poly-alcohols because of their faint acid properties, and this fact is made use of in the preparation of alkaline oxidizing solutions in which cupric ions are the oxidizing agents. These will be mentioned in connection with their use in the study of sugars.

Acrolein. The dehydration of glycerol follows the general rule that when hydrogen and hydroxyl groups are on adjoining carbon atoms, these may be removed by the use of a dehydrating agent or in some cases by the action of heat alone. In the case of glycerol two molecules of water are relatively easily removed.

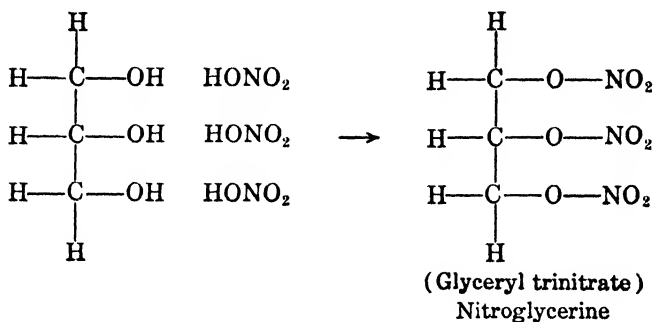


The above reaction takes place by heating the glycerol with sulfuric acid, potassium hydrogen sulfate, or phosphorus pentoxide, and is made use of as a test for glycerol or fats (which yield glycerol) since acrolein has a characteristic sharp and irritating odor. Acrolein (ă-krō'lē-în) or acrylic aldehyde (b.p. 52.7°) is produced industrially by the dehydrogenation of allyl alcohol over a copper catalyst. It has all the properties that would be suggested by its structure; it forms addition products with halogens and like other aldehydes is very easily oxidized, and polymerizes.

The production of "nitroglycerin" from glycerol is one of its most important uses, since tens of thousands of tons are produced annually. This substance, as is commonly known, is a high explosive and is used as such in the shooting of oil wells or may be mixed with other explosives. It is incorporated with wood

flour and nitrates to produce "*dynamite*." This may contain from ten to seventy per cent nitroglycerin (containing "nitroglycol") which is safer to handle in this form due to the cushioning and protective effect of the wood flour or other absorbing material used.

The formation of nitroglycerin takes place easily when glycerol is treated with a mixture of sulfuric and nitric acids. The temperature must be carefully controlled and it is unsafe to prepare more than very small quantities in the laboratory. The reaction takes place as follows:



The structure of nitroglycerin shows it to be an ester of nitric acid and glycerol. Its proper name is therefore *glyceryl trinitrate*. True nitro compounds have the nitro group (NO_2) directly attached to carbon (p. 213).

"Nitroglycerin" as an Explosive. An intimate mixture of charcoal, sulfur and potassium nitrate (black powder) explodes when ignited. This mixture contains an oxidizing agent (nitrate) and two reducing agents. The charcoal is not readily oxidized by the nitrate alone but the sulfur is more easily oxidized and helps set off the charcoal. If the ingredients are not mixed thoroughly the mixture will not explode, because the explosion is necessarily a rapid reaction and cannot take place unless the oxidizing agent comes in contact with the reducing agents within a short space of time.

Glycerol is a good reducing agent and if mixed with an oxidizing agent an explosive may result. If finely powdered potassium permanganate is mixed with dry glycerol, the mixture spon-

taneously inflames almost explosively. If the permanganate is not finely divided the reaction goes slowly. In the case of "nitroglycerin" the oxidizing agent and the reducing agent are not merely intimately mixed but are actually in the same molecule, so that there is opportunity for the reaction to take place very rapidly.

The explosion of nitroglycerin takes place very much more rapidly than the explosion of black powder, and the results of the two explosions may be quite different. For example, the very sudden formation of a large amount of gas between two rocks would have a tendency to shatter both the upper and the lower rocks in the vicinity of the charge, whereas if the formation of gas by the explosion were only moderately rapid, the upper rock might be lifted from the lower rock without breaking the lower rock. The difference in effect is the same as the difference between the effect of a sharp blow with a hammer and the effect produced by expending the same amount of energy in a steady push with a hammer. For different purposes, different types of explosives are desirable; for stumping powders, for example, it is desirable to have a relatively slow explosion. This is also true of propellants to be used in guns.

The value of an explosive for practical use depends by no means solely on its ability to explode, but also upon its non-explosiveness under conditions of manufacture, transportation and necessary handling. Thus the highest explosives known in some cases are absolutely worthless as such because they cannot be safely handled. The matter of cheapness is an important factor in this as well as all cases of practical application of chemistry. Glycerin from which nitroglycerin is made is available in large quantities at low prices, and hence is used. Since glycol has become available glycol dinitrate is also used as an explosive, generally mixed with nitroglycerin. Explosives which have some characteristics in common with nitroglycerin will be mentioned later.

Some of the most important explosives are very difficult to explode by ordinary means. They are therefore set off by *detonators*. Mercury fulminate and lead azide, $\text{Pb}(\text{N}_3)_2$, are

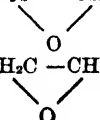
most often used for this purpose. They explode by percussion and their explosion sets up a vibration which causes the explosion of the main body of the explosive, which itself is not sensitive to ordinary shocks.

Most explosives which are of practical value liberate large amounts of gases when they explode, but this is not the invariable accompaniment of explosions, as silver acetylide (p. 61) is very explosive and the products are silver and carbon. If silver acetylide is exploded in a closed vessel it might, however, break the vessel through the very sudden heating and expansion of the air present. A part of the great destructive force of the atomic bomb is also the result of the sudden release of a tremendous amount of energy in the form of heat. In all cases of explosion there is a more or less sudden release of a large amount of energy.

A FEW POLYHYDRIC ALCOHOLS

	M. P.	B. P.°	Solubility in		
			Water	Alcohol	Ether
Ethylene Glycol, $\text{CH}_2\text{OHCH}_2\text{OH}$	-17.4°	197.2	inf.	inf.	sl.sol.
Propylene Glycol, $\text{CH}_3\text{CHOH-CH}_2\text{OH}$	—	188	inf.	inf.	sol.
Pinacol, $(\text{CH}_3)_2\text{COHCOH}(\text{CH}_3)_2$ (p. 117)	38°	173	sol. c	v. sol.	v.sol.
Glycerol, $\text{CH}_2\text{OHCHOHCH}_2\text{OH}$	17°	290	inf.	inf.	insol.
Erythritol, $\text{CH}_2\text{OHCHOHCHOH-CH}_2\text{OH}$	126°	330	v.sol.	s.sol.	insol.
Arabitol, $\text{CH}_2\text{OH}(\text{CHOH})_3\text{CH}_2\text{OH}$..	102°	—	v.sol.	v.s.h.	insol.
Mannitol, $\text{CH}_2\text{OH}(\text{CHOH})_4\text{CH}_2\text{OH}$..	166°	295 (3.5 mm.)	sol.	s.sol.	insol.

DERIVATIVES OF GLYCOLS

	B. P.°	Solubility in		
		Water	Alcohol	Gasoline
Ethylene Glycol $\text{CH}_2\text{OHCH}_2\text{OH}$	197.2	inf.	inf.	s. sol.
Ethylene chlorohydrin $\text{CH}_2\text{OHCH}_2\text{Cl}$	129	inf.	inf.	sol.
Ethylene oxide $\text{H}_2\text{C} - \text{CH}_2$	10.7	inf.	inf.	sol.
				
Propylene oxide $\text{H}_2\text{C} - \text{CHCH}_3$	34.	41.	inf.	inf.

DERIVATIVES OF GLYCOLS

	B. P.°	Solubility in		
		Water	Alcohol	Gasoline
Methyl cellosolve $\text{CH}_3\text{OCH}_2\text{CH}_2\text{OH}$	125.0	inf.	inf.	inf.
Cellosolve $\text{C}_2\text{H}_5\text{OCH}_2\text{CH}_2\text{OH}$	135.	inf.	inf.	inf.
Butyl cellosolve $\text{C}_4\text{H}_9\text{OCH}_2\text{CH}_2\text{OH}$	170.7	inf.	inf.	inf.
Cellosolve acetate $\text{C}_2\text{H}_5\text{OCH}_2\text{CH}_2\text{CO}_2\text{CH}_3$	156.	22.	inf.	inf.
Diethylene glycol $\text{HOCH}_2\text{CH}_2\text{OCH}_2\text{CH}_2\text{OH}$	244.5	inf.	inf.	s. sol.
Dioxan $\text{O} \begin{array}{c} \diagup \text{CH}_2\text{CH}_2 \diagdown \\ \diagdown \text{CH}_2\text{CH}_2 \diagup \end{array} \text{O}$	101.5	inf.	inf.	inf.
Carbitol $\text{C}_2\text{H}_5\text{OCH}_2\text{CH}_2\text{OCH}_2\text{CH}_2\text{OH}$	202.	inf.	inf.	inf.
Butyl carbitol $\text{C}_4\text{H}_9\text{OCH}_2\text{CH}_2\text{OCH}_2\text{CH}_2\text{OH}$	231.	inf.	inf.	inf.
Carbitol acetate $\text{C}_2\text{H}_5\text{OCH}_2\text{CH}_2\text{OCH}_2\text{CH}_2\text{CO}_2\text{CH}_3$	218.	inf.	inf.	inf.
Triethylene glycol $\text{HOCH}_2(\text{CH}_2\text{OCH}_2)_2\text{CH}_2\text{OH}$	288.	inf.	inf.	s. sol.
Ethylene dichloride $\text{CH}_2\text{ClCH}_2\text{Cl}$	83.5	.87	inf.	inf.
Ethylene diamine $\text{CH}_2\text{NH}_2\text{CH}_2\text{NH}_2$	117.2	inf.	inf.	s. sol.
Ethanolamine $\text{HOCH}_2\text{CH}_2\text{NH}_2$	172.	inf.	inf.	s. sol.
Triethanolamine $(\text{HOCH}_2\text{CH}_2)_3\text{N}$	208.	inf.	inf.	s. sol.

(10mm.)

PROBLEMS

1. Write the structural formulas for all the di-, tri- and tetra-alcohols with four carbon atoms per molecule.

2. Write the structural formula and calculate the percentage composition of the organic substance formed when acetyl chloride in excess acts upon glycerol.

3. Construct the structural formulas for the first three members of the homologous series of glycols, including isomers if there are any.

4. Among other products there may be formed by the oxidation of glycerol (a) a di-alcohol acid, (b) an alcohol di-acid, (c) a ketone di-acid. Write the formulas for these compounds.

5. Is there sufficient oxygen in nitroglycerin to oxidize completely all the carbon and hydrogen to carbon dioxide and water, supposing nitrogen gas to be the form in which the nitrogen appears in the reaction products? Supposing that nitrogen, carbon dioxide and water are products of explosion and that the excess oxygen, if any, remains in the form of oxygen gas, how many moles of gas would be formed from 0.5 mole of nitroglycerin?

6. Explain in terms of vapor pressures why glycerin can be distilled under diminished pressure at temperatures lower than 290° .

7. Hydroxyacetone may be formed under certain conditions by the dehydration of glycerol. Picture how this may take place in accordance with reactions already studied.

8. Ethyl alcohol may be regarded as the mono-hydroxyl substitution product of ethane; similarly glycol is a di-hydroxyl substitution product of ethane. Note the boiling points of ethane, ethanol and glycol and the effect produced by the introduction of hydroxyl groups. Which has more effect on the boiling point, the introduction of the first or the second hydroxyl group? Can you find any case in which the replacement of a hydrogen by a hydroxyl group does not raise the boiling point of the compound?

9. Write the formula for tetraethylene glycol and indicate how it may be prepared.

10. Epichlorhydrin has the formula $\text{H}_2\text{C}-\text{CH}-\text{CH}_2\text{Cl}$. Indicate



how it may be made from glycerol.

11. Ethylene oxide can hydrolyze or ammonolyze in only one way. Propylene oxide can ammonolyze in two ways. Explain.

12. Indicate how the amine $(\text{C}_2\text{H}_5)_2\text{NC}_2\text{H}_4\text{OH}$ might be prepared.

13. With how much acetyl chloride will one mole of diethanolamine react?

14. No isomer of glycerol is known. A structure of a possible isomer is $\text{CH}_2\text{OHCH}_2\text{CH}_2\text{OH}$. Indicate a *possible* method for the preparation of this compound and note the difficulties that would be encountered.

CHAPTER XVI

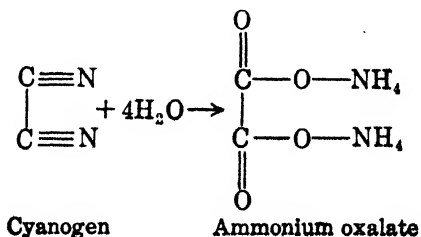
DICARBOXYLIC ACIDS

The dicarboxylic acids, as their name indicates, have two carboxyl groups in the molecule, and hence have two hydrogen atoms which are capable of ionization and of being replaced by metals. Sometimes the unfortunate term "dibasic" is applied to such acids to suggest that each molecule of the acid is capable of neutralizing two equivalents of a base.

Oxalic acid is the simplest and most important dicarboxylic acid derived from paraffin hydrocarbons. In certain plants (*oxalis*) it is found in the form of its potassium acid salt which gives the leaves a very sour taste. It also occurs naturally elsewhere in the form of its salts.

It is formed by the oxidation of glycol especially by nitric acid; in addition, it is formed when many organic substances such as sugars or starch or cellulose are oxidized with the same reagent. Oxalic acid is ordinarily fairly easily oxidized, and is therefore a good reducing agent, but it is able to withstand the oxidizing action of nitric acid, and hence many oxidations with nitric acid stop at this point, whereas if other oxidizing agents are used, complete combustion is likely to result. This effect is probably in part due to the fact that as a rule substances in ionic form are more easily oxidized, and nitric acid because of its acid character represses the ionization of oxalic acid (effect of common hydrogen ion) and thus makes it less susceptible to oxidation. Nitric acid does oxidize oxalic acid slowly.

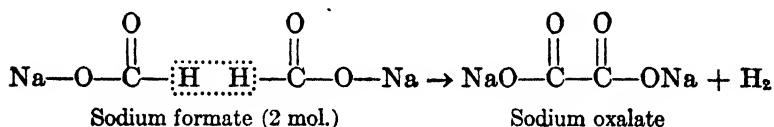
By the hydrolysis of cyanogen gas, oxalic acid or rather ammonium oxalate is formed.



This is exactly analogous to the hydrolysis of other cyanides and cyanogen is sometimes called the "nitrile" of oxalic acid.

Oxalic acid has been made technically by the treatment of sawdust or wood shavings with strong lye solution (sodium or potassium hydroxide) which brings about decomposition and leaves oxalic acid in solution in the form of its sodium or potassium salts. The oxalic acid is next precipitated in the form of its insoluble calcium salt by the addition of lime, and the oxalic acid is then obtained from the calcium salt by treatment with sulfuric acid. Final purification of oxalic acid may be accomplished by sublimation or by recrystallization.

The modern method for the production of oxalic acid consists of heating sodium formate to nearly 400°. The sodium formate itself is made by the interaction of sodium hydroxide and carbon monoxide.



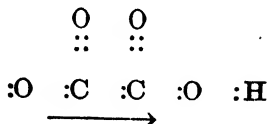
At the temperature used to promote this reaction, there is probably a dissociation of the formic acid whereby hydrogen atoms separate from the rest of the molecule. This allows the two hydrogen atoms to come together in a more stable form as hydrogen gas, and the two carbon atoms unite.

Oxalic acid is used principally by laundries as an acid rinse to remove iron stains and as a bleaching agent for leather and straw goods and for woodwork which has become discolored. Oxalic acid may also be used to eradicate ink spots, especially those caused by the "permanent" blue-black inks containing iron. It is used in photography and dyeing, and as a reagent in chemical laboratories.

Oxalic acid is one of the stronger organic acids. Like other di-acids oxalic acid molecules dissociate in two stages. In tenth normal solution about 60 per cent of the molecules are dissociated into hydrogen and acid oxalate ions (OOCCOOH). In addition there is a very slight ionization of the acid oxalate ions into hydrogen ions and doubly negative oxalate ions. This second

ionization is very slight because the negative charge of the acid oxalate ion prevents the positive hydrogen ion from separating.

The electrons in the acid oxalate ion are displaced by repulsion in the direction of the arrow in the figure, by the unneutralized electron left on the oxygen.



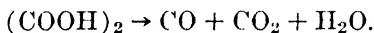
In dicarboxylic acids in which the carboxyl groups are separated from each other by several carbon atoms, this displacement of electrons is negligible in its effect on the separation of the second hydrogen ions and as a consequence the formation of doubly negative ions takes place comparatively much more readily than in oxalic acid.

Oxalic acid is capable of forming two series of salts, acid salts and normal salts. It is also able to form mono- and di-esters, a mono-amide, HOOCCONH_2 , known as *oxamic acid*, a di-amide, $\text{H}_2\text{NOCCONH}_2$, known as *oxamide*, and a di-chloride *oxaly chloride*, ClOCCOCl . *Methyl oxalate* is unlike many of the simple esters in that it is a solid at ordinary temperature. It is volatile, however, and can be distilled. *Calcium oxalate* is very insoluble and for this reason and perhaps others, oxalic acid and its soluble salts are poisonous. They precipitate calcium salts which are present in the tissues and thus upset necessary equilibria.

The oxidation of oxalic acid to carbon dioxide and water is easily accomplished quantitatively by the use of oxidizing agents such as permanganates. Hence oxalic acid and its salts, which can be obtained in pure form, are used as standard reducing agents for the standardization of oxidizing solutions. *Potassium tetraoxalate*, $\text{KHC}_2\text{O}_4\text{H}_2\text{C}_2\text{O}_4 \cdot 2\text{H}_2\text{O}$, is one compound which is used in this way. This substance probably does not exist in solution, but only in crystalline form. Equimolecular quantities of acid potassium oxalate and oxalic acid crystallize together with water of crystallization. This particular salt is valuable because it is obtainable in pure form and can be handled and

weighed directly without taking up or giving off water or changing in any way, due to contact with the air. Potassium tetraoxalate can also be used as a standard acid for standardizing solutions of strong bases, as each formula weight is capable of neutralizing three equivalents of alkali.

With two carboxyl groups in the same molecule there might be a possibility of the formation of an inner anhydride of oxalic acid. If there is such an anhydride formed by dehydration of oxalic acid with concentrated sulfuric acid, it immediately breaks down to carbon dioxide and carbon monoxide.



It has previously been noted that when two adjoining carbon atoms are attached to oxygen or other non-metallic element, they break apart easily.

Homologous Series. Oxalic acid is the first and most important member of a homologous series of dicarboxylic acids. Other acids in this series will not be discussed individually in detail, but several of the normal acids are included in the accompanying table. There are several isomers among the higher dicarboxylic acids, for example, eight such isomers of sebacic acid are known.

NORMAL DICARBOXYLIC ACIDS

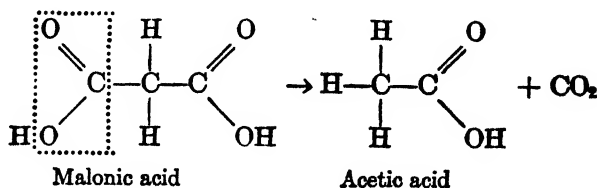
Acid	Formula	M. P.°	Sol. in 100 gm. water (20°)	Ionization constant (primary)	Per cent pri- mary ioniza- tion in .1 N solution
Oxalic...	COOHCOOH	187	8.6	(.10)	(62.)
Malonic..	COOHCH ₂ COOH	135.6	73.5	.00163	12.
Succinic..	COOH(CH ₂) ₂ COOH	187	5.8	.000068	2.5
Glutaric..	COOH(CH ₂) ₃ COOH	97.5	63.9	.0000475	2.1
Adipic...	COOH(CH ₂) ₄ COOH	153	1.5	.0000365	1.9
Pimelic..	COOH(CH ₂) ₅ COOH	105.5	5.	.000034	1.8
Suberic..	COOH(CH ₂) ₆ COOH	140	.16	.0000296	1.7
Azelaic..	COOH(CH ₂) ₇ COOH	108	.24	.0000253	1.6
Sebacic..	COOH(CH ₂) ₈ COOH	135	.10	.0000234	1.5

The peculiar fact should be noted that the melting points are lower and the solubilities in water are higher in the case of the acids containing uneven numbers of carbon atoms. These two

properties are closely related since the same forces that hinder melting also tend to prevent solution. The contrast between the "even" and "odd" acids is less in the higher members.

A probable reason for the differences between the "odd" and "even" dicarboxylic acids is revealed when models of the acids are made. It is found in the zigzag models that the two carboxyl groups lie on the same side of the chain in the "odd" acids and on opposite sides in the "even" acids. This structural difference and the difference in orientation of the molecules which results probably causes the observed effects. The strengths of the acids decrease rather regularly with the increase in number of carbon atoms, so that the higher acids are only a little stronger than the corresponding fatty acids.

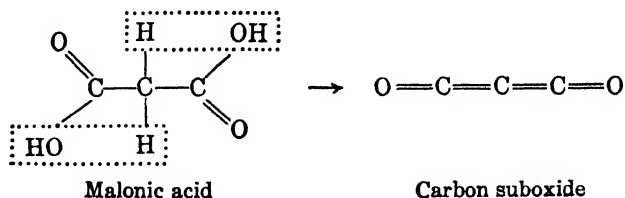
Malonic acid, $\text{COOHCH}_2\text{COOH}$, the second member of the series, like many other acids with an uneven number of carbon atoms, probably does not occur in nature. Its esters have been used in certain syntheses which will be mentioned in Chapter XIX because of the relationship to *acetoacetic ester* which is discussed at that point. The central carbon atom which is joined to two carboxyl groups holds both the hydrogen atoms and the carbon atoms rather loosely. In the malonic ester syntheses, which are to be discussed later, the mobility of the hydrogen atom comes into play. When malonic acid is heated above its melting point it decomposes liberating a molecule of carbon dioxide, showing the weakness of the union between carbon atoms.



This latter reaction is common to all acids in which a carbon atom is attached to two carboxyl groups.

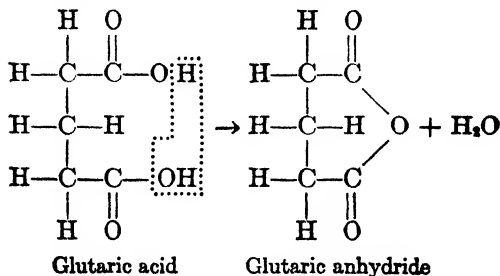
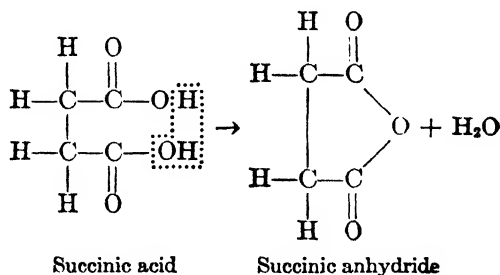
The dehydration of malonic acid is interesting because an unusual product is formed. In the malonic acid molecules there are hydrogen atoms and hydroxyl groups attached to adjoining

carbon atoms, and these are removed by phosphorus pentoxide in a manner analogous to the formation of ethylene from alcohol.



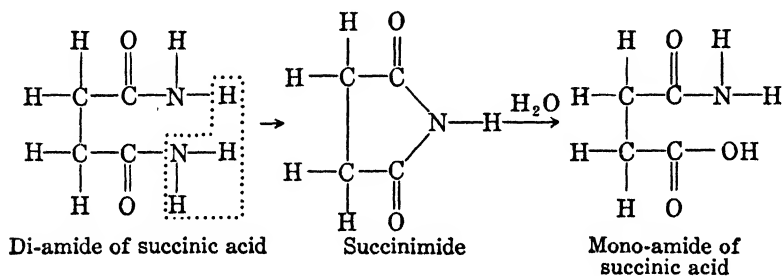
The product, *carbon suboxide*, C_3O_2 , is a gas which reacts readily with water to form malonic acid and polymerizes, forming a dark red solid. In behavior and structure carbon suboxide is like the ketenes.

Succinic acid gets its name from the fact that it can be obtained from amber (Lat., *succinum*). It occurs rather widely in nature. It is one of the products formed in alcoholic fermentation. Both succinic and glutaric acids which have **respectively** four and five carbon atoms per molecule lose water when heated (succinic more easily), forming inner anhydrides of the acids as indicated.

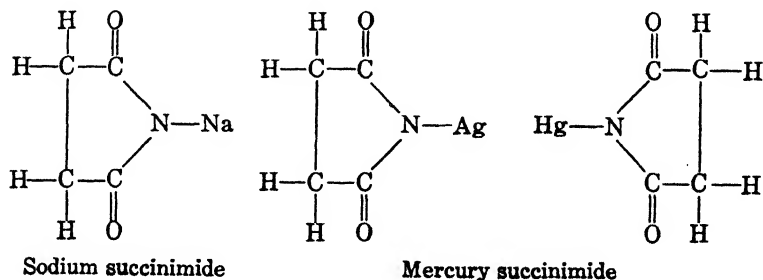


These anhydrides, compounds with five and six membered rings, are quite stable as compared with ring compounds with fewer members in the ring. They can be hydrolyzed, however, just as other anhydrides, and produce the acids from which they are derived. In the case of succinic anhydride moist air will effect the hydrolysis.

When the di-amide of succinic acid is heated, ammonia is lost, just as water is lost in case the acid is heated. The resulting compound is *succinimide*. This imide, like the amides, is capable of hydrolysis, and produces the mono-amide of succinic acid. Glutaric acid derivatives undergo similar reactions.

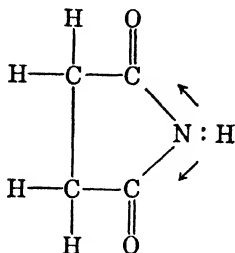


It is interesting to note that succinimide has slight acid properties and can form metallic derivatives such as the following:



It has been noted that ammonia in anhydrous condition has very faint acid properties. The presence of the two carbonyl groups attached to the nitrogen causes a displacement of electrons toward the oxygen as indicated and thus increases the tendency of the nitrogen to give off hydrogen ions (acidic property), and at the

same time decreases its tendency to add on hydrogen ions, which is associated with its basic property.

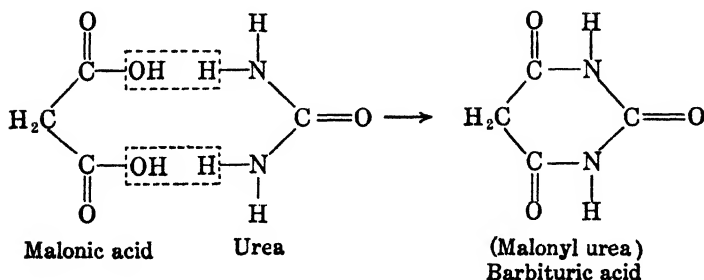


In alcoholic solution alkalis are definitely neutralized by succinimide, since as an acid it is only a little weaker than hydrocyanic acid.

Mercury succinimide has at present substantially replaced corrosive sublimate (HgCl_2) for the sterilization of surgical instruments because it is less corrosive.

Barbituric Acid and Its Derivatives. Certain compounds derived from dicarboxylic acids are of sufficient importance as medicinal products to merit discussion at this point.

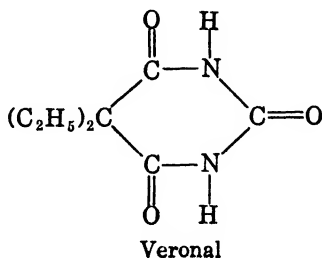
Corresponding to the acid amides which may be regarded as *acyl ammonias* (acetamide is acetyl ammonia) there are the *ureids* which are *acyl ureas*. Dicarboxylic acids condense with urea in such a way as to eliminate two molecules of water and produce cyclic ureids. The ureid derived from malonic acid and urea is indicated below.



Barbituric acid is not itself important in medicine but several of its derivatives are. Its distinct acid properties may be due to

the imino groups ($=\text{NH}$) which are in close proximity to several acid forming carbonyl groups. There is also the possibility that the acidity is due to tautomeric forms in which hydrogen has migrated to oxygen.

Barbital or veronal, one of the most important soporifics or sleep-producing drugs, is diethyl barbituric acid. It is prepared by condensing the diethyl ester of diethyl malonic acid with urea, in the presence of sodium ethylate.



Phenobarbital (Luminal) is a similar drug and its structure is exactly like veronal except that a phenyl group (C_6H_5) replaces one of the ethyl groups.

Amytal is similar in structure except that the *isoamyl* group replaces one of the ethyl groups in veronal. It is widely used for oral administration especially mixed with *pyramidon* (p. 580) which is an efficient analgesic (relieves pain). There are hundreds of closely related compounds which have somewhat similar properties.

The above drugs act in somewhat similar ways but have their individual peculiarities. They are not habit forming to the same extent as are opiates and as a rule are not analgesic but induce sleep by "quieting the nerves." Their use is not free from danger.

PROBLEMS

1. Ordinary succinic acid is one of two isomeric dicarboxylic acids. Write the formula for the isomer which is known as isosuccinic acid. How would this acid decompose on heating?

2. What results from the ammonolysis of succinic anhydride?

3. Write the formulas for the following: (a) malonyl chloride monoethyl ester; (b) ethyl oxamic ester; (c) methyl oxalic chloride; (d)

ethylene oxalic ester; (di-ester of glycol). These are a few examples of the many known derivatives of the dicarboxylic acids.

4. How many cubic centimeters of .2 N alkali solution will be neutralized (a) by one gram of anhydrous oxalic acid? (b) by one gram of potassium tetraoxalate?

5. What is the relation between a normal solution of oxalic acid as a reducing agent and a solution which is normal as an acid?

6. Before synthetic methanol came into use methyl alcohol was often freed from acetone by converting it into its oxalic acid ester, a solid which is purified and hydrolyzed. How much methyl alcohol and oxalic acid could theoretically be obtained from 10 grams of dimethyl oxalate?

7. One gram of oxalic acid is treated with sulfuric acid and the evolved gases are bubbled through and allowed to stand over strong sodium hydroxide solution. Neglecting the vapor pressure of the alkali solution, what should be the volume of the gas at standard conditions? Will carbon monoxide react with sodium hydroxide under these conditions to form sodium formate?

8. How could ethylene dibromide be used as a starting material in the synthesis of succinic acid?

9. In acid solution how much potassium permanganate is required to oxidize two grams of sodium oxalate?

10. What would be formed by the hydrolysis of cyanoacetic acid?

11. What would be formed by the action on carbon suboxide of (1) ammonia, (2) methanol?

12. Diethyl malonate can be reduced to a glycol. How can ammonium glutarate be prepared from this?

13. Ethylene is produced by the electrolysis of sodium succinate. Picture how this may take place (p. 141). How might propylene be produced by electrolysis?

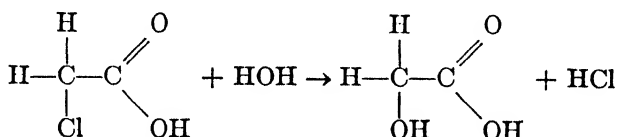
14. If sodium succinimide is treated with ethyl iodide and the resulting compound is hydrolyzed what is produced? A preparative method similar to this will be mentioned later.

15. If monomethyl succinate is electrolyzed dimethyl adipate results. Picture how this happens.

CHAPTER XVII

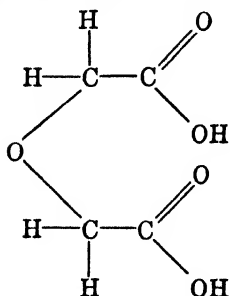
HYDROXY ACIDS

Some of the most important organic acids from the standpoint of natural occurrence are the hydroxy or alcohol acids. They very frequently are responsible for the sour taste of fruits, berries, etc. The simplest acid of this type is **glycolic** (gli-kō'lik) **acid**, CH_2OHCOOH (hydroxyacetic acid). It has been mentioned as an oxidation product of glycol and is also formed by the hydrolysis of chloroacetic acid. Chloroacetic acid is both an acid and an ester of hydrochloric acid; by hydrolysis of the ester-acid, an alcohol-acid and hydrochloric acid are produced.

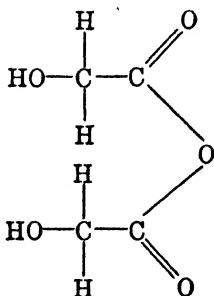


Hydroxyacetic acid is itself not particularly important as a naturally occurring acid, but has been found in unripe grapes. It is a stronger acid than acetic acid, and almost as strong as formic acid. The increase in strength over that of acetic acid may be explained on the basis of the displacement of electrons toward the oxygen of the hydroxyl group, and the consequent increase in ionization of the hydrogen of the carboxyl group.

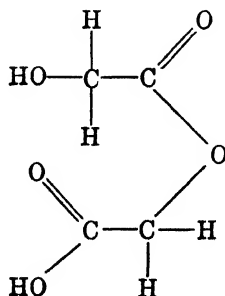
Glycolic acid has all of the properties of an acid and an alcohol and is therefore able to form the corresponding derivatives. The following represent the structures of the various anhydrides of glycolic acid, all of which are known.



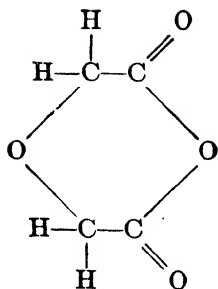
I. An ether-di-acid



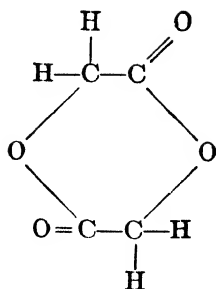
II. A di-alcohol-acid anhydride



III. An alcohol-ester-acid



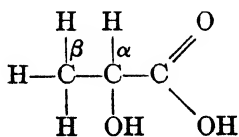
IV. A cyclic
ether-acid
anhydride



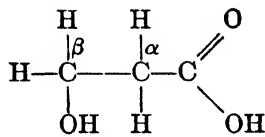
V. A cyclic
di-ester

All of these substances in general show the properties which would be expected of compounds of the types represented. Glycolic acid does not form a simple inner ester for the same reason that glycol does not form an inner ether; ring compounds with less than five members in the ring do not form readily.

Hydroxypropionic Acids. There are two hydroxy acids derived from propionic acid.

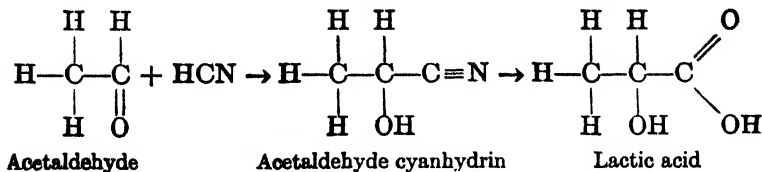


α -Hydroxypropionic acid



β -Hydroxypropionic acid

The first which has a hydroxyl group on the carbon atom next to the carboxyl group is called α -hydroxypropionic acid, or *lactic acid*. The second is called β -hydroxypropionic acid, or *hydracrylic acid*. Lactic acid can be shown to have the structure represented by formula I because it can be made by hydrolysis of the cyanhydrin derived from acetaldehyde and hydrocyanic acid.

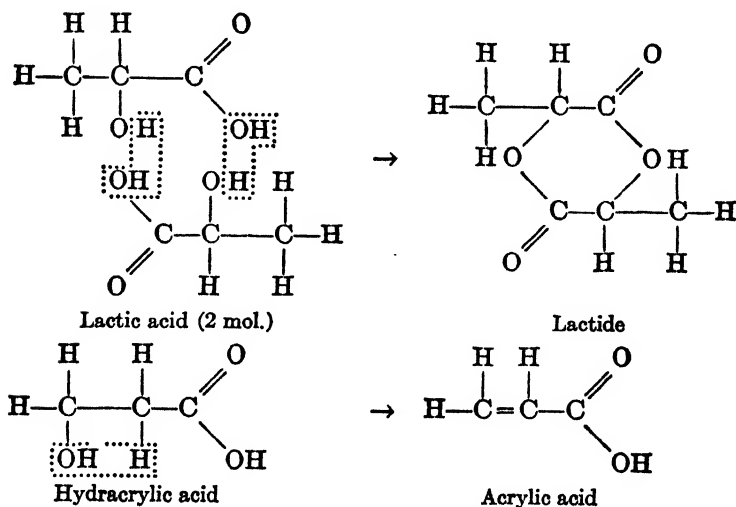


Hydracrylic acid can also be synthesized by methods which show its structure. In addition to the two hydroxypropionic acids mentioned there is an α,β -dihydroxypropionic acid which is called *glyceric acid* because it is an oxidation product of glycerol. All three of these hydroxypropionic acids are stronger than propionic acid as shown in the table.

	Ionization constants	Per cent ionized .1 N solution
$\text{CH}_3\text{CH}_2\text{COOH}$	0.000134	1.1
$\text{CH}_3\text{CHOHCOOH}$	0.0014	3.7
$\text{CH}_2\text{OHCH}_2\text{COOH}$	0.0003	1.7
$\text{CH}_2\text{OHCHOHCOOH}$	0.0023	4.9

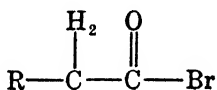
The effect of the proximity of the hydroxyl to the carboxyl group is clearly shown.

The behavior of lactic and hydracrylic acids on heating is interesting. Lactic acid forms, with loss of water, a cyclic inner ester, called *lactide*, while hydracrylic acid forms an unsaturated acid.

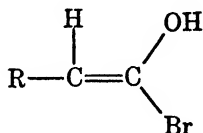


These reactions are characteristic of α - and β -hydroxy acids in general.

α -Hydroxy acids can be prepared through α -bromo acids which in turn are made from the fatty acids by the Hell-Volhard-Zelinsky reaction which involves treating the anhydrous acids with bromine in the presence of phosphorus. The acid bromide is first formed

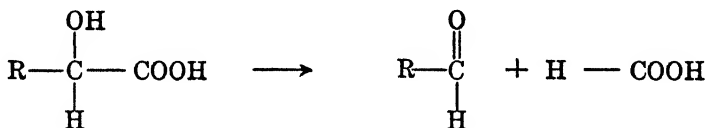


which probably enolizes



adds bromine and then decomposes to yield the α -bromo derivative. Chlorine can be used instead of bromine.

The α -hydroxy acids when heated decompose into formic acid and an aldehyde. This serves as a method for determining lactic acid since the acetaldehyde produced can be readily determined.



Stereoisomerism. If the structure of lactic acid is viewed from the standpoint of the arrangement of atoms in space, rather than the usual graphic formulas in two dimensions, a very interesting situation presents itself. If the four valences of carbon are symmetrically arranged in space, and if each of these four valences is attached to a different atom or group, two different spacial arrangements are possible. These can readily be shown by the use of models, examples of which are pictured in the following figures.

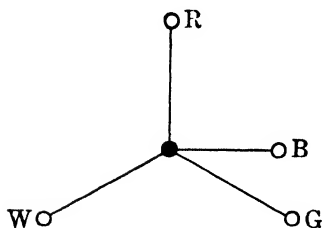


Fig. I

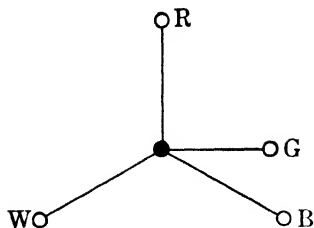


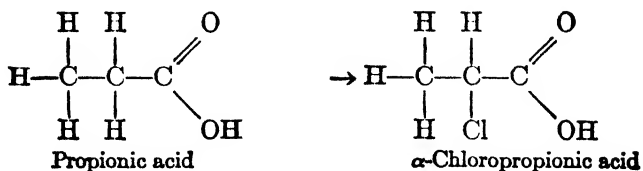
Fig. II

Let the black ball indicate a carbon atom which is attached to four different groups or atoms arranged symmetrically in space, represented by balls of different colors, white, red, blue and green. Though each of the two models shows the same groups attached to the carbon atom, they are so arranged that one cannot be superimposed on the other in a manner such that all parts correspond each to each. If figure II is moved to the left without rotation, it may be placed so that the red ball on figure I corresponds to the red ball, figure II; similarly the white corresponds to the white, but the blue and green balls are crossed, and there is no position in which all of the colors correspond. The two models have the relationship to each other that a mirror image has to the object, or that the left hand has to the right. If any two of the balls in each model were the same color, then only one arrangement would be possible.¹

¹ The situation that confronts us will be clearer if we relate it to certain facts of everyday life. Tools and utensils and implements in general can be placed in two categories, *i.e.*, those that suit left and right handed people equally well and those that are constructed for one group only or have to be adapted if used by both groups. To the former belongs hammers, axes, table forks, knives, etc. In the latter class are included the older type desk telephones, golf clubs, scythes, scissors, etc. Observation will show that all objects belonging to the first group possess a plane of symmetry, that is, it is possible to imagine them cut by a plane into two equivalent halves. Those which are necessarily either right handed or left handed possess no plane of symmetry. They are asymmetric and their mirror images are not superimposable on the object. The same condition exists with molecular structures, some are *symmetric* (including most of those considered up to this point) others are *asymmetric*. Whenever a carbon atom is attached to four different groups it lacks a plane of symmetry.

In lactic acid we have a situation like that shown in the models, in that one carbon atom is attached to four different groups or atoms. Such a carbon atom is said to be *asymmetric*. A strict adherence to the theory of spacial structure would lead us into the prediction that there should be two lactic acids, which, however, should be identical in chemical properties. For example they should be acids of exactly the same strength, because they both contain carboxyl groups which are related in exactly the same way, in each individual case, to the hydrogen atom, to the methyl group, and to the hydroxyl group. In a similar way the alcohol properties of the two substances should be the same, for the relation of the hydroxyl group to the rest of the molecule as a whole is the same in the two cases. Likewise the methyl groups and the hydrogen atom in the two compounds should behave exactly alike. In short, all of the chemical actions of the two lactic acids should according to the predictions be exactly alike. Physical properties which depend on composition and arrangement, such as solubility and melting point, would also be expected to be the same for the two substances.

Suppose one were to prepare lactic acid starting with propionic acid. What should the relation of the product be to these two hypothetical forms of lactic acid? Propionic acid does not contain a carbon atom which is attached to four different groups, and therefore there should be only one possible arrangement of propionic acid. In α -chloropropionic acid, however, which may be made by chlorination of propionic acid (p. 259), there is a carbon atom which is attached to four different groups, and hence two different kinds should be possible according to the theory.



If the reaction is followed by the use of models instead of two dimensional formulas, it will be noted that there are two positions in which chlorine may replace hydrogen, and that the products

formed in the two cases have the same relation to each other as the models pictured above. In propionic acid there could be no directing force which would cause one of the hydrogen atoms to be replaced in preference to the other, because the two hydrogen atoms are situated exactly alike in regard to the rest of the molecule. If it were possible to isolate a single molecule of propionic acid and chlorinate it separately it would have to form a molecule of one or the other of the forms. However, with a large number of molecules the reaction should go partly in one way and partly in the other, depending solely on how the molecules happened to come together. When a large number of molecules is concerned, as is always the case experimentally, there would be formed, according to the rules of probability, equal numbers of molecules of each type. When these molecules are hydrolyzed to give lactic acid, the hydroxyl groups would take the place of the chlorine and equal amounts of the two forms of lactic acid would result, so that synthetic lactic acid should be a mixture of the two possible forms of lactic acid.

Existence of Two Forms of Lactic Acid. These predictions as to the existence of two kinds of lactic acid with exactly the same chemical properties, and the prediction that in synthesis equal amounts of the two forms should be produced, are both interesting and important, because they are exactly in accord with the facts. Two forms of lactic acid with exactly the same chemical properties and the same solubilities are known, and by synthesis we get a mixture of equal amounts of these two forms.

How do we know that there are different forms of lactic acid? In what ways are they different, and in what ways can the two forms be separated? These are important questions which must be answered. In muscle is found lactic acid which is sometimes called, for this reason, *sarcolactic acid* (Gr. *sarx*, flesh). By the action of certain organisms on sugar there is formed a lactic acid which is not identical with the lactic acid found in muscle. It is exactly like it in all chemical properties, in solubility in all solvents, in melting point, etc., but does differ from it in one optical property; namely, in its *optical* activity or effect on plane polarized light.

Optical Activity. For the purposes of our discussion a beam of light may be compared to a cylinder, with vibrations in all planes passing through the axis of the cylinder. On the same basis plane polarized light is a ribbon, in which the vibrations are limited to one particular plane through the axis of the cylinder. Light is changed from ordinary light to plane polarized light, or in other words is "polarized," when it passes through a tourmaline crystal or through a "nicol" prism or through "polaroid" (p. 265). A nicol prism is made from iceland spar in such a way that only the so-called "extraordinary ray" is able to pass through. Since the extraordinary ray is plane polarized, only the light vibrating in a certain plane passes through the prism. If the light which has been polarized is allowed to strike a second nicol prism, it will pass through only if the second nicol prism is in a certain position with respect to the first. When the second nicol prism is in such a position that the light going through the first will not pass through the second, the two nicol prisms are said to be "crossed."

If a solution of sarcolactic acid is placed between two crossed nicol prisms, it will be found that light passes through the second prism to some extent, and that if the second nicol prism is rotated a little it will be brought back to the position where light does not pass through. Suppose the ribbon of polarized light at first is in a horizontal plane, and that the second nicol prism shuts off all light coming in this plane. The effect of the solution of sarcolactic acid is to twist the ribbon of polarized light so that when it emerges it is no longer in a horizontal plane, but is inclined a little, and the second nicol prism allows some light to pass. If the second nicol prism is rotated through a few degrees, the light fails to pass through and the amount of rotation necessary to bring it to this position is the amount of rotation of the plane of light caused by the sarcolactic acid.

An arrangement of two nicol prisms with devices for measuring the angles through which the polarized light is turned, comprises what is known as a *polariscope*, *polarimeter*, *saccharimeter*, etc., depending on the exact construction.

The amount of rotation caused by the lactic acid depends on the concentration of the solution, and upon the length of the

solution traversed by the light. It is proportional to the actual amount of optically "active" substance, through which the light passes. If instead of the sarcolactic acid the other kind is interposed between the crossed nicol prisms, the effect is exactly the same except that sarcolactic acid twists the ribbon of light in a clockwise direction while the other kind twists the beam in a counter-clockwise direction. In equal concentrations and equal lengths of solution the two different kinds of lactic acid rotate the plane of polarized light exactly the same amount but in opposite directions.

A mixture of equal amounts of the two forms of lactic acid, such as is always obtained when the substance is prepared in the laboratory by synthetic methods, and such as is present in sour milk, does not rotate a beam of polarized light in either direction and is therefore spoken of as optically "inactive." Both "active" forms of lactic acid occur in nature, and if these are mixed in equal quantity the mixture is identical to synthetic lactic acid.

Though optical activity and isomerism were first noted in organic compounds which contain asymmetric carbon atoms, later study has revealed that many compounds of other elements exhibit the same phenomena. It has been observed in compounds containing asymmetric atoms of nitrogen, phosphorus, platinum, lead and certain other elements. The study of geometrical isomerism, including many cases in which optical activity has no bearing, is sometimes called "stereochemistry."² The ability of a liquid or a solution to rotate a beam of polarized light is usually dependent on the presence of an asymmetric atom in the molecules, but may be due to an asymmetry of the molecule as a whole as in special cases to be mentioned later.

Optical activity of substances *in crystalline form* is quite different, and is dependent upon the structure of the crystal rather than upon the structure of the molecules of the substance. Substances in different crystal systems may rotate polarized light, but these substances when melted or brought into solution are optically inactive unless the molecules themselves are asymmetric.

² See A. W. Stewart, "Stereochemistry," Longmans, Green & Co.

Polaroid. Within the last few years, light-polarizing screens (Polaroid) have been produced wherein the polarizing media consist of oriented distributions of submicroscopic crystals of certain materials such as iodoquinine sulfate in a binder such as a cellulose plastic film. This type of film gives the effect of a single large crystal and is generally supplied in bonded form between two pieces of glass in a manner similar to safety glass.

Rotatory Powers. For purposes of comparison the rotatory power of a substance may be expressed in terms of its *specific rotatory power*, which is a constant quantity only at a definite temperature, and with a definite wave length of light. As a matter of fact the specific rotatory power may also vary with the concentration of the solution but this may often be neglected unless precise measurements are to be made. The rotatory power also varies with the solvent, and this factor should be specified; water is understood to be the solvent unless it is specified otherwise.

The specific rotatory power (α) of a substance in solution is defined in the following mathematical relationship:

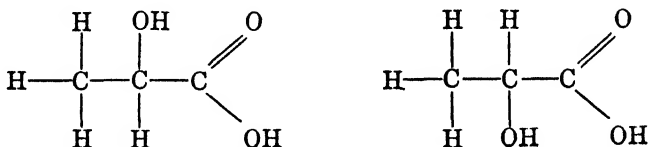
$$\alpha = \frac{r}{cl},$$

in which r is the observed angular rotation, c is the number of grams of the substance in 1 ml. of solution, and l is the length of the observation tube in decimeters. In other words the specific rotation is the rotation which would theoretically be produced by one decimeter of a solution, containing one gram of the optically active substance in one milliliter of solution. The *molecular rotatory power* of a compound is the specific rotatory power multiplied by the molecular weight.

Separation of Lactic Acids. It has been found that certain microorganisms destroy and utilize sarcolactic acid as a food while other organisms utilize the other lactic acid. By choosing the proper organisms either one of the optically active forms can be obtained from a mixture. Other means whereby the optically active forms may be separated is left for later discussion. Lactic acid is an exceptional case in this particular, since both forms occur in nature and both forms may be acted on by organisms.

The majority of optically active compounds occur in nature only in one form, and the other form is not utilized by organisms as a food. In the case of poisonous substances, etc., neither form, of course, is used by organisms.

Terminology and Formulation. *d*-Lactic acid (dextro, right) and *l*-lactic acid (levo, left) are the names commonly used to designate the two forms of lactic acid. Projections of space formulas, such as those shown below, may be used to designate them.



These formulas are assigned in a purely arbitrary manner because it is not known, for example, which represents the *dextro* acid. Two substances whose structures have the relationship of object to mirror image, as above, are spoken of as *optical antipodes*.

The kind of isomerism exhibited by the two lactic acids is the most important type of *geometrical isomerism* or *stereoisomerism*. The term *optical isomerism* is applied to this and similar cases because of the optical difference between the isomers. Most of what has been said about the isomerism of the two lactic acids may be applied generally to substances of the same type in which there is an asymmetric carbon atom, that is, a carbon atom which holds four different atoms or groups. All substances containing asymmetric carbon atoms are capable of existing in optically isomeric forms.

Production and Uses of Lactic Acid. Inactive lactic acid is made commercially by the fermentation of sugars. Its formation by fermentation is of importance in the manufacture of yeast, in the souring of cream for churning, in the ripening of cheese, in making sauerkraut, and in the fermentation of silage for stock food. As sold commercially it is a viscous liquid containing about 80 per cent acid. It finds its chief uses in the form of its antimony, zinc and iron salts which are used in dyeing.

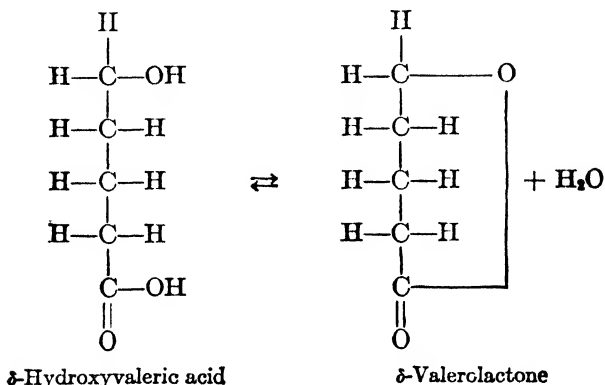
It is also used in the leather industry, in foods, beverages and candies and in the plastics industry.

Glyceric acid, α,β -dihydroxypropionic acid, is formed by the careful oxidation of glycerol with nitric acid. This acid has in its structure an asymmetric carbon atom and hence should be capable of existing in two optically active forms. The synthetic product made either by the oxidation of glycerol or by other means is optically inactive, for the same reasons that apply to synthetic lactic acid. If a solution of synthetic ammonium glycerate, $\text{CH}_2\text{OHCHOHCOONH}_4$, is inoculated with a common mold known as *Penicillium glaucum*, the salt of the *dextro* acid is used as a food by the mold and the salt of the *levo* acid remains unchanged in the solution, and from this the *levorotatory* acid can be obtained. This action is not unique, and illustrates the fact that optical antipodes may act physiologically like two entirely different substances.

β -Hydroxybutyric acid, $\text{CH}_3\text{CHOHCH}_2\text{COOH}$, is an acid the *dextro* form of which is of some importance in physiology as it is produced in the body along with acetone and a ketone-acid, *acetoacetic acid*, $\text{CH}_3\text{COCH}_2\text{COOH}$, when the oxidation mechanisms of the body are deranged. Normally these substances are probably intermediate products in the oxidation, particularly of fats, to carbon dioxide and water. In disease, the oxidation may be incomplete and result in their presence in abnormal amounts in the blood, and finally in the urine. The occurrence of these substances in the urine as waste products is indication of a pathological condition. It is interesting to note that when butyric acid itself is oxidized with hydrogen peroxide, β -hydroxybutyric acid is produced; the oxidation with this reagent does not proceed on the carbon atom next to the carboxyl group, but attacks the second carbon atom. This is an example which shows that different oxidizing agents may have their individual peculiarities of action.

Hydroxy Derivatives of Higher Fatty Acids—Lactones. A large number of hydroxy derivatives of the higher fatty acids are known but none is of sufficient importance to be discussed in detail. There are four possible mono-hydroxy derivatives of

normal valeric acid. These may be designated as α , β , γ , and δ -hydroxyvaleric acids, the Greek letters indicating the position of the hydroxyl group with relation to the carboxyl group. The γ - and δ -acids are able to form inner esters. These cyclic esters are formed under much the same conditions as other esters. They are often very stable (the equilibrium favors the ester) so that they cannot be effectively hydrolyzed by water. In an alkaline medium they are converted to the salts of the hydroxy acids.



Inner esters of this type are known as *lactones*.

Malic acid is hydroxysuccinic acid, $\text{COOHCHOHCH}_2\text{COOH}$, and is so named because it was first isolated from unripe apples (Latin *malum*, apple). It was discovered in 1785 by Scheele,³ and has since been shown to be one of the most widely distributed substances in the vegetable kingdom. It is found in fruits, seeds, leaves and roots of a great many plants, more often in the form of its salts. It is one of the important substances concerned in the physiology of plants. Evidence for its structure may be obtained by heating the malic acid with hydriodic acid which is used for reduction of alcoholic hydroxyl groups (p. 103). When treated in this manner succinic acid is produced,

³ K. W. Scheele (1742-1786) was an early Swedish chemist of great note. Among the elements and compounds discovered by him are oxygen, chlorine, arsine, glycerol and hydrocyanic acid. He described the properties of hydrocyanic acid, including its taste, but apparently did not know of its poisonous properties.

and since there is only one position for the alcoholic hydroxyl group to occupy the structure above is indicated. As the formula shows, malic acid has an asymmetric carbon and exists in two optically active forms.

The form of malic acid which occurs so abundantly in nature has a rotatory power which changes from slightly positive (*dextro*) to negative when a concentrated solution is diluted.

Rotatory Power and Chemical Structure. Theoretically, since optical activity is definitely attributed to the asymmetry of carbon (or other) atoms it should be possible to link up the *magnitude* of the rotatory power with the *degree* of asymmetry. Several attempts have been made to do this, but only with qualified success. The amount of rotation produced by a particular asymmetric carbon atom is dependent in part upon the differences in the weights of the atoms or groups attached to the asymmetric atom. It has been possible in some cases to calculate the approximate rotatory powers of compounds on this basis. There are other factors which also enter in, however, such as the character of the groups (position of the center of gravity, affinity for electrons, etc.) and perhaps their attraction for each other. Another factor which unquestionably is of importance is the effect of the solvent upon the optically active substance. Solvents may cause "association" of molecules to varying extents and in addition may combine loosely with different solutes in varying degrees, and perhaps bring about other modifications which may appear to be of minor consequence but which may affect the rotatory power very appreciably.

It is not surprising, therefore, that the rotatory power of a substance in dilute solution is in general somewhat different from its rotatory power in concentrated solution. The same substance in different solvents may show rotatory powers which are not only different in degree but also in direction of rotation. Temperature also affects the degree of rotation as might be expected. Conversion of an acid into its salt may cause a profound change in rotatory power. The salts of *levo* lactic acid, for example, are *dextro*-rotatory, while the salts of the *dextro* acid are *levo*-rotatory. It is to be noted that if the rotatory power of one of two

antipodes changes in one direction because of the effect of a different solvent or temperature, etc., the other antipode changes its rotatory power an equal amount in the opposite direction, so that under the same conditions their optical activity is always equal and opposite in direction.

When the optical rotatory powers of a homologous series of esters, which are very similar chemically, are compared, a rather regular variation is observed. The following molecular rotatory powers (specific rotatory power \times molecular weight) of a series of esters of *d*-amyl alcohol will illustrate the case.

	Mol. rotation °	Differences °
Amyl formate	+304	
Amyl acetate	+429	125
Amyl propionate	+520	91
Amyl butyrate	+554	34
Amyl valerate	+566	12
Amyl caproate	+582	16

A somewhat similar case has been observed in the case of esters of tartaric acid which is to be discussed shortly. The rotatory powers of the esters in all cases were measured directly, not in solution.

When there is more than one asymmetric carbon atom in a molecule the effects of the different atoms are additive, provided, of course, the substances compared are not too different chemically and the same conditions are used. The molecular rotation of diamyl ether is thus approximately twice that of amyl alcohol. Provided sufficient care is taken in comparing similar substances under similar conditions, the study of rotatory powers may throw much light on chemical structure.

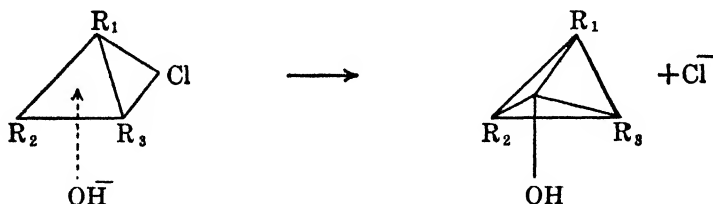
Walden⁴ Inversion. A phenomenon of theoretical as well as practical interest in connection with optical activity was first observed among derivatives of malic acid. Walden found that when *levorotatory* chlorosuccinic acid was converted into malic acid by the action of silver hy-

⁴ P. Walden (1863-) did a large portion of his work in the field of physical chemistry studying dielectric constants, theories of solution and optical rotation. The Walden inversion was discovered in 1895. Formerly Walden was at the Polytechnic Institute in Riga, Russia; but in recent years has been at the University of Rostock, Germany.

droxide and then reconverted into chlorosuccinic acid using phosphorus pentachloride, the chlorosuccinic acid formed was principally the *dextro* rather than the *levo* acid which was the starting material. The *dextro* chlorosuccinic acid on similar treatment yields *levo* chlorosuccinic acid. Evidently an "inversion" takes place during the transformations.

It has not been possible to determine with certainty and to the satisfaction of everyone at which point the inversion occurs, because of the fact that in such cases inversion is *liable* to take place whenever one atom is exchanged for another one that is *directly* attached to the asymmetric carbon atom. Thus if lactic acid is changed into its ethyl ester one can be sure that the resulting ester has the same configurational relationship as the original acid. This seems a reasonable result and no difficulties arise from such an assumption. If, however, lactic acid is converted into chloropropionic acid, one of the valences of the asymmetric atom is involved and experience has shown in such cases that no dependence can be placed on the conclusion that the product has the configuration corresponding to the original acid.

Indeed there is considerable reason for thinking that inversion is the *normal* result in reactions of this type and that the peculiarity of the reaction involving chlorosuccinic acid resides in the fact that inversion has happened only once, whereas if inversion had taken place *twice*, it would not be detected since the starting and final chlorosuccinic acids would then be identical. This may be what happens when sodium or potassium hydroxides are substituted for silver hydroxide above. The experimental result is that the use of these reagents leads to the formation of a product identical with the original. The results obtained with silver (or mercury) hydroxide may then be "abnormal" in a sense, which is in line with the behavior of other silver compounds (p. 208).



The mechanism of the inversion (which may be the normal behavior) may be presumed to involve the collision of a hydroxyl ion (in the particular case under discussion) with what corresponds to the face of the tetrahedron opposite the chlorine atom. This may cause the separation of the chlorine as an ion and the attachment of the hydroxyl in such a way as to yield the inverted configuration. A. R. Olson has presented evidence to indicate that this inversion is a common mechanism of reactions whether asymmetric atoms are involved or not. Thus

when methyl chloride undergoes hydrolysis the hydroxyl group may take a position opposite in configurational relations to that occupied by the chlorine. Since the molecules are not asymmetric such inversion is not apparent.

The problems involved in the Walden inversion are fundamental and their solution is difficult. Further experimentation in addition to the large volume already done will be necessary before the essential points are satisfactorily settled.

It should be clear that the inversions brought about as indicated above are quite distinct from the conversion of an optically inactive substance into an active one. The latter has not been accomplished except through the intervention of some optically active compound.

Tartaric Acids. Among the most important and commonly occurring acids in the vegetable kingdom is tartaric acid. It occurs in varying amounts in a good many fruit juices, but its most important occurrence is in grape juice, from which the acid potassium salt separates out during fermentation. The German name of the acid, "*weinsäure*," indicates its origin. This crude crystalline precipitate is called "*argol*" and from it is obtained pure acid potassium tartrate or what is commonly called *cream of tartar*. Tartaric acid has the structure COOHCHOHCHOHCOOH , and having two carboxyl groups is able to form acid, normal, or mixed salts.

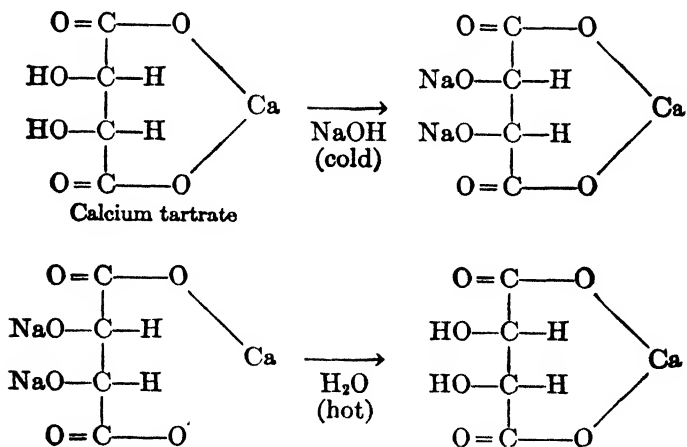
Cream of tartar is extensively used as a constituent of baking powder. Tartaric acid itself is fairly strong compared with other organic acids, as might be expected from the groups present, and its acid salt is still acidic enough to liberate carbon dioxide from the carbonates. The active ingredients of cream of tartar baking powders are cream of tartar which acts as the acid, and sodium bicarbonate which furnishes the carbon dioxide. The reaction involved is the following.



The salt formed in this process, sodium potassium tartrate, may be made by neutralization of the acid salt with sodium hydroxide and crystallizes readily with four molecules of water of crystallization. It is known commonly as *Rochelle salt*, and is used as a laxative. This salt is one of the ingredients of

Fehling's solution which is an important reagent used in studying the sugars. *Seidlitz powders* consist of (1) a mixture of sodium bicarbonate with Rochelle salt, and (2) tartaric acid. The two powders are dissolved separately and when mixed, carbon dioxide is given off, which makes the laxative more palatable than it would otherwise be.

Calcium tartrate is nearly insoluble in water, and its precipitation is the basis of a qualitative test for tartaric acid and its salts. It is distinguished from calcium oxalate, by the fact that it is soluble in cold potassium or sodium hydroxide but precipitates when the solution is heated to boiling. This peculiar behavior may be explained by the reaction of the strong alkali on the alcohol groups in the calcium tartrate, to form a soluble salt-like compound, which is hydrolyzed in hot water, thus causing a reprecipitation of the calcium tartrate. Salts are always more completely hydrolyzed in hot water than in cold because water is more highly ionized at higher temperatures. The reactions may be indicated as follows:

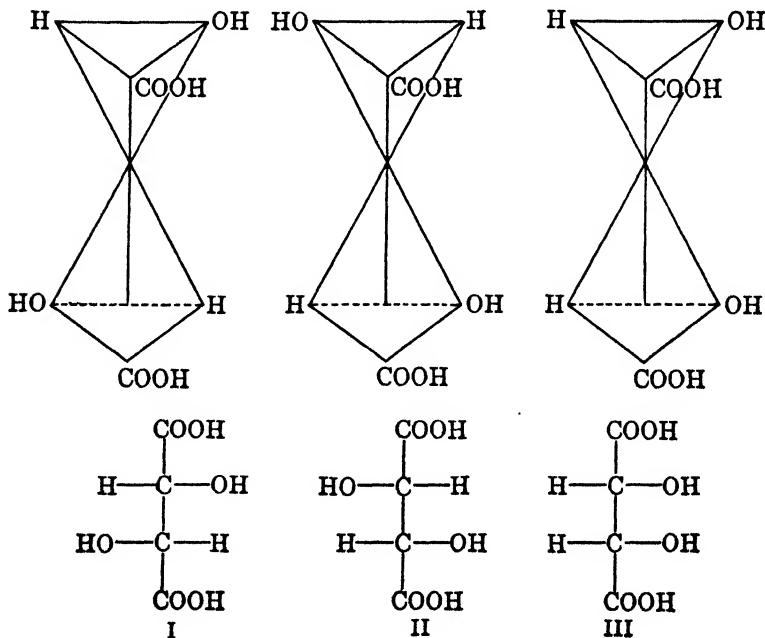


Other salts of tartaric acid are able to react with alkali, and therefore show un-neutralized acidity in the alcohol groups. Rochelle salt or sodium potassium tartrate is not only able to react with strong alkalis but also reacts with and dissolves a number of metallic hydroxides forming alcoholates. It is because

of this property that it is used in Fehling's solution, in which $\text{Cu}(\text{OH})_2$ is dissolved, as will be explained later. *Potassium antimonyl tartrate*, $\text{COOKCHOHCHOHCOO}(\text{SbO}) \cdot \frac{1}{2}\text{H}_2\text{O}$, goes under the name of *tartar emetic* and has been used in medicine to induce vomiting as the name implies. It is also used as a mordant in dyeing.

Stereochemistry of the Tartaric Acids. Ordinary tartaric acid which is obtained from natural sources is only one of the known varieties of tartaric acid. It is *dextrorotatory*, and an inspection of the formula shows that there are two asymmetric carbon atoms in the molecule.

A manipulation of models representing molecules in which there are two asymmetric carbon atoms, each of which are attached to the same kinds of groups, shows that there are three and only three distinct arrangements possible. These may be represented by the following diagrams and projection formulas:



The consideration of the models will also show that in the case of **III** the upper half of the model is the mirror image of the lower half. Thus if one of the asymmetric carbon atoms in this form rotates polarized light in one direction, the other would rotate the light in the opposite direction an equal amount. The result is that the molecule as a whole has no effect on polarized light. If we pass from hydroxyl to carboxyl to hydrogen in either upper or lower half of projection formula **I**, the direction is counter-clockwise. In formula **II** the direction is clockwise, passing from one group to another in the same order. In formula **III**, however, the order of these groups is clockwise in the lower half and counter-clockwise in the upper half. The same results are obtained by inspection of the models, provided the point of observation is the point where the two tetrahedra are joined.

There is a form of tartaric acid which corresponds to this latter structure, known as **mesotartaric acid**. In the form of anhydrous crystals, it melts at 140° . It crystallizes also with one molecule of water of crystallization. Mesotartaric acid is optically inactive, and cannot by any means be separated into optically active components. To do this the two asymmetric carbon atoms would necessarily be separated, and this would mean a breaking down of the molecule.

Ordinary tartaric acid is *dextrorotatory*, and may be represented by either formula **I** or **II**. If formula **I** be arbitrarily chosen for the *dextro* acid, then formula **II** will represent *l*-tartaric acid, its optical antipode. These two forms of tartaric acid are exactly alike except in the *direction* of rotation of the plane of polarized light and in the action of organisms upon them. Both *dextro* and *levo* tartaric acid melt at 170° and have identical solubilities, etc., just as is true for the lactic acid. It should be noted that optical *isomers* do not always have the same physical and chemical properties, for this is true only of optical *antipodes* whose structures have the relationship of object and mirror image. Thus mesotartaric acid is not the optical antipode of either of the two other forms, and therefore although it re-

sembles the others in chemical properties, there are easily distinguishable differences, especially in physical properties. This fact might be predicted from a careful consideration of models, but cannot well be clarified here.

Conversion of One Form of Tartaric Acid to Another.

When ordinary *d*-tartaric acid is subjected to action of high temperature in the presence of water, the increased molecular motion apparently causes the valence forces to loosen so that the groups leave their attachments to some extent, and recombine in the most probable manner. Thus when ordinary tartaric acid is heated to about 175° for some time or boiled with alkali, the result is an optically inactive mixture of *d*- and *l*-tartaric acids and mesotartaric acids. The heating of *l*-tartaric acid or mesotartaric acid yields the same results: Although it is easy to convert an optically active substance into an inactive mixture, the conversion of an optically inactive mixture into an active compound is quite a different process. The situation is somewhat comparable to the conversion of kinetic energy into heat and vice versa. Kinetic energy (ordered motion) can quite easily be converted into heat energy (disordered motion), but the reverse can be accomplished only incompletely.

Racemic Acid. If a mixture of equal amounts of *d*- and *l*-tartaric acid is dissolved in water and made to crystallize through evaporation or cooling, the resulting crystals containing water of crystallization melt at 205-6° instead of at the melting point of either the *dextro* or *levo* acid (170°). This crystalline substance is known as *racemic acid*, and consists of equal amounts of *l*- and *d*-tartaric acids *crystallized together*. The union of both types of molecules is probably similar to the case of the alums. When potassium sulfate and aluminum sulfate in equimolecular proportions are put into solution and allowed to crystallize, the potassium aluminum sulfate or alum, which crystallizes out, is different in physical properties from either the potassium sulfate or aluminum sulfate. In solution the two kinds of molecules are probably not chemically combined in the ordinary sense, but when allowed to crystallize, go together to make up definite crystals.

In fermented grape juice there is, in addition to the potassium acid salt of the ordinary *d*-tartaric acid, some of the corresponding salt of the *levo* variety. The crude tartrates which crystallize out of the fermented juice are partly in the form of a crystallographic union of the *d*- and *l*-forms of the acid potassium salt. This crystalline substance is known as *acid potassium racemate*. Other salts of the two forms of tartaric acid crystallized together are also known as racemates.

Racemic acid thus is readily obtained from natural sources, and because of its historical importance some of the terminology in regard to optical activity is derived from its name. Conversion of a *d*- or *l*-compound into an inactive mixture is spoken of as *racemization*. A mixture of a pair of *d*- and *l*-substances such as is obtained by synthetic methods is called a *racemic mixture*. When the *d*- and *l*-forms crystallize together after the manner of racemic acid the resulting substance is sometimes called a *racemic compound*.

Pasteur⁵ in his pioneer work on optical activity worked with racemic acid. He converted it into its sodium ammonium salt, and found that on crystallization he did not get single crystals of sodium ammonium racemate, but got a mixture of crystals, distinguishable only by the fact that one set of crystals had the relationship to the other set of object to mirror image. This of course would have escaped the eye of any but a trained observer. He succeeded in picking out and separating by hand the two kinds of crystals and made the remarkable discovery that when one set of crystals was dissolved in water they gave a *dextrorotatory* solution and the other set gave a *levorotatory* solution. Mixing equal quantities of these two kinds of crystals in solution produced an inactive solution identical with the original solution. This discovery laid a foundation for much that was to follow in the study of optical activity, eventually for the theory

⁵ Louis Pasteur (1822-1895) was a famous French scientist, who made important contributions to the fields of physics, chemistry, bacteriology and medicine. His work with tartaric acids was done in 1861. The student is referred to a biography of this world-famous scientist—R. Vallery-Radot, "Life of Pasteur," Doubleday, Page and Co.

of LeBel and Van't Hoff,⁶ that optical activity is caused by asymmetric carbon atoms.

Resolution of Optically Active Substances. By this method of Pasteur, it is then possible to separate a mixture of *d*- and *l*-tartaric acids into the two varieties of tartaric acid, but it is very laborious and not practicable. It cannot be used as a general method for other substances, because it is not always possible to get two sets of crystals. The two forms may crystallize together. It is only below 28° that the sodium ammonium salts crystallize in separate *enantiomorphous* crystals; above this temperature single crystals of sodium ammonium racemate form.

The process of obtaining the optically active forms from an inactive mixture is spoken of as a *resolution* of the optically inactive mixture. As has already been mentioned, the two forms of lactic acid and the two optically active forms of tartaric acid are different in their relationships to organisms. Thus *l*-lactic acid may serve as a food for a certain mold, while *d*-lactic acid does not. Similarly *d*-tartaric acid may serve as a food for this same mold (*Penicillium glaucum*) while *l*-tartaric acid does not. Thus if a solution of racemic acid is inoculated with this mold, *d*-tartaric acid is consumed while *l*-tartaric acid is left unaltered by the organism and may be isolated from the solution. This is a method which may in some cases be used to obtain *one* of the varieties from an inactive mixture. In some cases it is the *levo* form which is left and in other cases it is the *dextro* form and there is no means of predicting in a given case which will be utilized. In many cases of optically active compounds, only one of the forms is found in nature. In these cases the form which occurs in nature, and is hence more important, is utilized as a food by organisms. Besides the limitations already mentioned

⁶ J. A. LeBel (1847-1930) and J. H. Van't Hoff (1852-1911) were both students of Wurtz in Paris, and independently conceived the idea of the asymmetric carbon atom. Both published their conclusions in 1874. Van't Hoff was at this time only 22 years old, and in his treatise set forth remarkably well the essentials of stereochemistry. Van't Hoff was Dutch but in later life held a professorship at the University of Berlin. His principal work was in the field of physical chemistry. LeBel was a Frenchman and maintained a private laboratory in Paris.

this method has the additional disadvantage that it cannot be applied to any substance which is incapable of acting as a food for some organism. It cannot be used to resolve *dl*-mixtures of poisonous substances.

Utilization of Optically Active Bases. The complete resolution of an inactive mixture into its optically active components is in general a difficult, laborious and long drawn out process. There are some cases in which it may be accomplished without great difficulty. The only method which is ordinarily practicable involves the use of some naturally occurring, optically active compound. In nature, substances which have in their structure asymmetric carbon atoms generally occur as one of the optically active forms rather than as an inactive mixture. Examples of substances which are used most in this connection for resolution of acids are *quinine*, *strychnine*, *brucine* and other alkaloids. The substances will be studied later, and it is sufficient for our present purpose to know that they are ammonia derivatives, contain asymmetric carbon atoms in their structure and occur naturally, either in the *d*- or *l*-forms.

As an example let us indicate how *l*-strychnine may be used to resolve an inactive mixture of lactic acids. Both forms of the lactic acid are identical in chemical properties and each kind will therefore act with the *l*-strychnine to form a salt, since the strychnine is basic and unites with acids. From the *d*-lactic acid there is formed the *l*-strychnine *d*-lactate, while from the *l*-lactic acid, *l*-strychnine *l*-lactate is formed. These two salts are optical isomers, but they are not optical antipodes; their structures do not have the relationship of object to mirror image. The lactate parts of the molecules have the relationship of object to image, while the strychnine residue in both molecules is identical. The fact that the two salts are not antipodal in structure gives the two salts slightly different properties, and makes it possible to separate them by *fractional crystallization*.

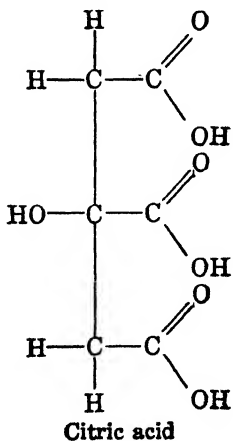
This consists first in bringing the mixture of salts into solution and causing crystallization to take place. One of the salts will be less soluble than the other, so that the first crop of crystals that comes out of solution will contain a larger proportion of the less soluble kind of substance. The mother liquor will contain a

larger proportion of the more soluble form. Hence a partial separation is accomplished. By repeating this process on the different "fractions" obtained eventually complete separation may be effected.

The separation is complete when two fractions are obtained with an equal and opposite rotatory power, which does not change on recrystallization. During this process of fractional crystallization a good deal of material will inevitably be lost. The efficiency of the process depends on the difference in the solubilities of the two salts that are to be separated. Often only one of the two forms is recovered in pure state. After the strychnine salts of the two forms of the acids are separated, they may be separately reconverted into the optically active acids.

It is obvious that the application of the alkaloids in this manner cannot be made to substances which will not react with the alkaloids. If other naturally occurring substances are available which will react with the particular compound which it is desired to resolve, they can be used. Naturally occurring *d*-tartaric acid for example may be used in a manner similar to that described above, for the resolution of *dl*-mixtures of alkaloids or other base forming substances, or for the resolution of optically active alcohols.

Citric acid is a monohydroxy tricarboxylic acid, represented by the following structural formula.



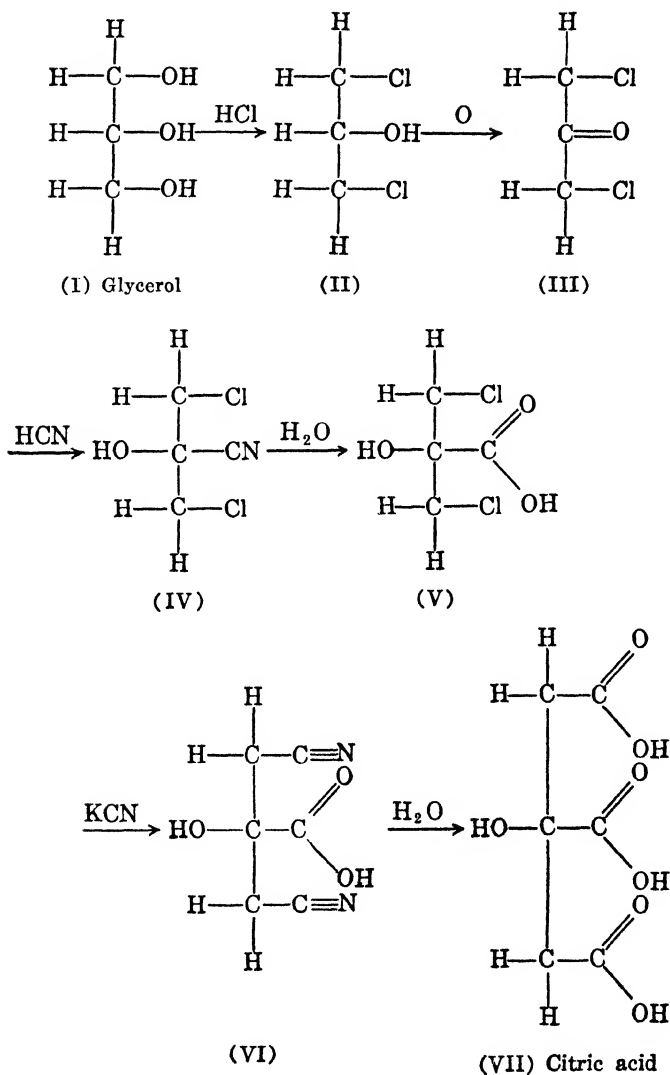
It is important because of its occurrence in many fruits, notably in the citrus fruits. It has been prepared on a large scale from the juice of lemons in which it occurs up to as high as six per cent of the juice. The juice is neutralized with calcium carbonate forming tricalcium citrate (sit'rāt), which is purified by taking advantage of the fact that it is less soluble in hot water than in cold. The calcium salt is decomposed with sulfuric acid forming calcium sulfate and the free citric acid which crystallizes from the solution after removal of the calcium sulfate.

The action of certain organisms (*Citromyces pfefferianus* and *Citromyces glaber*) upon glucose produces citric acid in relatively high concentration. Use is made of this fact in the commercial preparation of citric acid.

Citric acid with one molecule of water of crystallization loses water on heating. The anhydrous acid melts at 153°. It is the most widely used organic acid in the food and beverage industry. Citric acid and its salts are laxative; magnesium citrate is especially useful since the citric acid is combined with magnesium which itself is laxative. About 27,000,000 pounds of citric acid were produced in 1946.

Ferric ammonium citrate is mixed with potassium ferricyanide as a coating for "blue print" paper. When ferric ammonium citrate is exposed to strong light, part of the citric acid is oxidized by the ferric iron, which in turn is reduced to ferrous iron. Upon treating the paper with water after exposure to light, ferrous ferricyanide or Prussian blue is precipitated wherever the ferrous salt has been formed. Unexposed portions of the paper are washed free from the soluble salts and become white. The salt of citric acid is used for this purpose because it has been found that the oxidation-reduction reaction involved is quite sensitive to the action of light.

If the formula given above is correct, citric acid could not rotate polarized light, and since citric acid is always inactive its behavior is in accord with the formula given. The synthesis of citric acid can be accomplished starting with glycerol, according to the following scheme. This method of formation proves that it must have the structure indicated.



Other hydroxy acids which are related to the sugars will be mentioned in a later chapter.

PROBLEMS

1. The specific rotatory power of cane sugar is 66.5° at 20° . How much rotation of polarized light would be caused by its passage through 20 cm. of a solution containing 2.9 g. sugar per 100 ml. solution?

2. Can two optical antipodes be separated by fractional crystallization? Why? May mesotartaric acid be separated from *l*-tartaric acid by this means?

3. Might (*a*) the monoethyl ester of mesotartaric acid, (*b*) the ethylmethyl ester of mesotartaric acid, be optically active?

4. If you should consider racemic acid to be a single chemical substance, how would its molecular weight compare with that of either *d*- or *l*-tartaric acid?

5. How many monoethyl citrates could exist? How many diethyl citrates? Construct formulas for each. How many of the esters pictured could exist in optically active forms?

6. Tartaric acid exists in three distinct forms. In how many forms might the acid, $\text{CH}_3\text{CHOHCHOHCOOH}$, exist? Would there be an inactive meso form?

7. Would you expect the salts of naturally occurring malic acid to be optically active? Can you predict whether they are *levo*- or *dextro*-rotatory?

8. When ordinary lactic acid is heated theoretically three different lactides should be formed. What are their relationships?

9. Would γ -valerolactone or δ -valerolactone exist in optically active forms? Would an optically active lactone lose its activity on hydrolysis?

10. There are two monohydroxy tricarboxylic acids isomeric with citric acid which have no asymmetric carbon atoms. Construct their formulas.

11. Taking into consideration the possibility of stereoisomerism, work out all possible structures for simple alcohols with four carbon atoms.

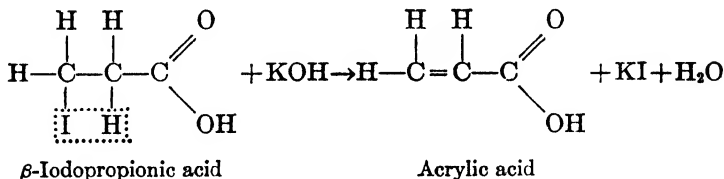
12. With the help of models work out the formula of a compound with two olefin double bonds on one carbon atom which is without asymmetric carbon atom but can exist in forms which are "mirror images" and not superimposable one on the other.

CHAPTER XVIII

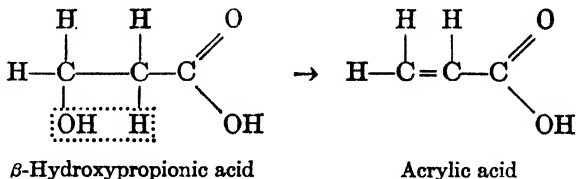
UNSATURATED ACIDS

It will be desirable to take space for the discussion of only a few of the known unsaturated acids; the student may thus gain the basic knowledge necessary for dealing with others of like kind.

Acrylic acid, $\text{CH}_2=\text{CHCOOH}$, is the simplest unsaturated monocarboxylic acid. It can be prepared by methods similar to those used for the preparation of ethylene. If β -iodopropionic acid is heated with an alcoholic potash solution, the effect is to split off hydriodic acid (which is neutralized by the alkali) forming the unsaturated acid.



Parallel with the analogous method of preparation of ethylene (p. 50), acrylic acid may also be prepared by the dehydration of β -hydroxypropionic acid. This is accomplished quite easily merely by heating the hydroxy acid until it decomposes into the unsaturated acid and water (p. 258).



These reactions show how general some of the simpler reactions are, and how close is the parallel between a simple unsaturated hydrocarbon and an unsaturated acid. Acrylic acid can

also be made by the careful oxidation of the corresponding unsaturated alcohol ($\text{CH}_2=\text{CHCH}_2\text{OH}$, allyl alcohol) and the unsaturated aldehyde ($\text{CH}_2=\text{CHCHO}$, acrolein). It has the properties common to unsaturated compounds; it can be reduced with nascent hydrogen to propionic acid and adds on halogens and halogen acids.

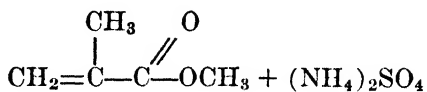
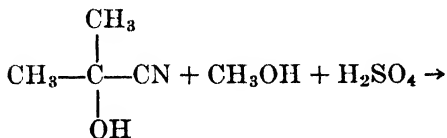
When halogen acids add on to the acid, the β -substitution products of the saturated acid are formed.



The above behavior is contrary to what might be expected since bromine would be expected to go to the carbon atom which holds the negative (electron pulling) carboxyl group. One explanation of this behavior is based upon the idea of conjugated partial valences (p. 289).

An interesting feature regarding the unsaturated acids is that they are considerably stronger than the corresponding saturated acids. Acrylic acid is about 2.4 per cent ionized in .1 *N* solution compared with 1.1 per cent for propionic acid. It seems quite the general rule that unsaturation is accompanied by an increase in acid properties. We found that the highly unsaturated hydrocarbon acetylene shows some acid properties while in the saturated hydrocarbons the acid property is lacking.

Methacrylic acid, $\text{CH}_2=\text{C}(\text{CH}_3)\text{COOH}$, may be prepared by several methods which are analogous to those used for the preparation of acrylic acid. The acid itself is not of great industrial importance but its esters, especially the methyl ester, are of interest because they can be polymerized to form a perfectly colorless resin. These methacrylate resins are sold under various trade names such as Lucite, Plexiglas and Crystallite. Methyl methacrylate is prepared in the following manner:



Maleic and Fumaric Acids. The unsaturated acids formed by the dehydration of malic acid are of particular theoretical interest. When malic acid, $\text{COOHCHOHCH}_2\text{COOH}$, is heated it undergoes dehydration like β -hydroxypropionic acid, but in this case there are formed two acids instead of one, as might be expected. One acid known as *maleic* (mă-lē'ik) *acid* melts at 130° and is readily soluble in water; the other acid, known as *fumaric acid*, does not melt but sublimes when heated to high temperature, and is difficultly soluble in water. Fumaric acid only is found in nature and gets its name from its occurrence in the sap of *Fumaria officinalis*. Both of these acids show unsaturated properties, and when reduced with nascent hydrogen they produce the same substance: succinic acid. It seems that here we have two substances with different properties, and only one formula for both substances.

The difficulty disappears when we turn to the space formulas for the two substances. Two possible spacial structures for the substances are pictured below.

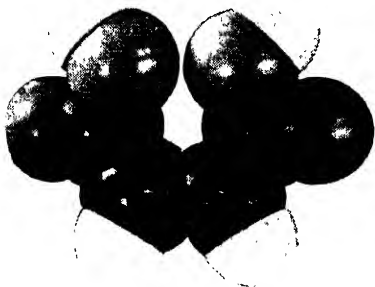


FIG. I. Model for maleic acid

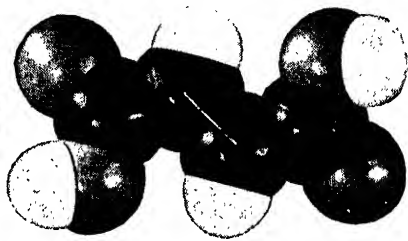
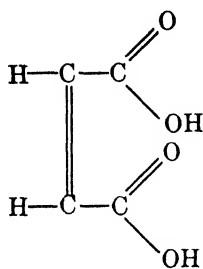


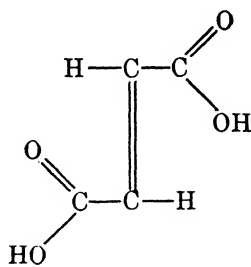
FIG. II. Model for fumaric acid

The situation can be grasped if one imagines the two central carbon atoms (see also I and II below) held by a double linkage so that freedom of rotation around the axis joining them does not exist. In the models, above, the two center black balls (carbon atoms) are held together rigidly by two linkages and hence in I the two white balls at the bottom (hydrogen atoms) must always maintain the indicated position with respect to each other and cannot take the positions shown in II, in which black balls

lie between them. Likewise in II the several balls representing the two carboxyl groups are necessarily held apart, and the two white balls at the ends (hydrogen atoms) cannot be made to touch each other. The projection formulas below with proper interpretation show the same relationship.



(I) Maleic acid



(II) Fumaric acid

There are then two possible structures and two known compounds. It remains to decide which formula belong to each substance. Fortunately there is one difference in the two acids which leaves little doubt on this point. Maleic acid, as the low melting, soluble acid is called, forms an inner anhydride quite easily merely by heating, whereas fumaric acid, the other acid, cannot be made to form an anhydride. If one deals with the models it will be readily apparent that it is impossible to construct a space model for the anhydride of the acid represented by structure II, and that a space model may be easily constructed for the anhydride of the acid with structure I. Only in structure I can the two carboxyl groups come into proximity.

There is still another conclusive reason why the structure for maleic acid must correspond to I and that of fumaric acid must correspond to II. By careful oxidation of these two unsaturated acids hydroxyl groups are added on to each end of the double bonds. By reference to models it will be clear that a substance with structure I upon oxidation in this way could produce only mesotartaric acid while a substance with structure II could produce only *d*- or *l*-tartaric acids. The facts are in accord with the theory and the isomerism and relationships of maleic and fumaric acids are therefore a striking confirmation of the struc-

ture theory and of the importance of spacial interpretation of formulas.

It is interesting to note that of the two acids maleic is considerably the stronger. This might be expected inasmuch as one carboxyl group generally reinforces the acid property of another, and in the case of maleic acid the two carboxyl groups are more closely related.

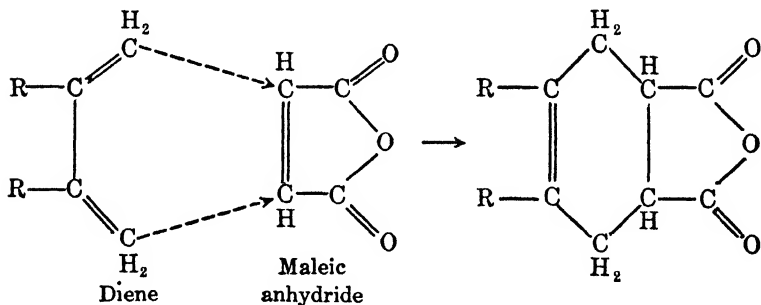
The student should be reminded that the relationship which we have here discussed holds for other compounds than the particular ones which have been chosen as examples. In order to have this type of isomerism there must be two doubly bonded atoms, which need not, however, be carbon atoms. Cases are known, which will be mentioned later, in which the doubly bonded nitrogen atoms are responsible for a similar result. It is also well to bear in mind that there are no asymmetric carbon atoms in these compounds and no possibility of optical activity or right and left hand relationship. The two compounds are not identical in chemical properties as are optical antipodes.

This sort of isomerism exhibited by maleic and fumaric acids is spoken of as *cis-trans* isomerism. Maleic acid has the "*cis*" form (Latin, on this side), fumaric acid the "*trans*" form (Latin, across). Both optical isomerism and *cis-trans* isomerism belong to a more general class of isomerism called *geometrical isomerism* or *stereoisomerism*. In both types of isomerism spacial arrangement comes into play but otherwise they are not related.

When malic acid is heated and undergoes dehydration a mixture of maleic and fumaric acids is formed. This is as would be expected, since inevitably the dehydration of each molecule must produce either maleic or fumaric acid and it would be expected that both would be formed. When a mixture of maleic and fumaric acids is heated the maleic acid forms its anhydride which distills off leaving the fumaric acid. If this residual fumaric acid is heated to a high temperature, eventually there is a shifting of atoms within the molecules and fumaric acid changes over slowly to maleic acid which forms the volatile anhydride.

Maleic acid and its anhydride though formerly of only theoretical importance can now be made cheaply by the vapor phase oxidation¹ of benzene. Maleic acid has been found to be an effective antioxidant (p. 487) for use in fats and oils, and there is the possibility of its use in various industries (leather, for example) as well as its conversion into fumaric and malic acid for use in food and other industries. It is used extensively in the production of resins, and in the production of succinic acid by hydrogenation.

Diels-Alder Reaction. Maleic anhydride undergoes one type of reaction which has been applied widely. It reacts with butadiene (p. 57), chloroprene (p. 395) and other conjugated dienes in the following manner:



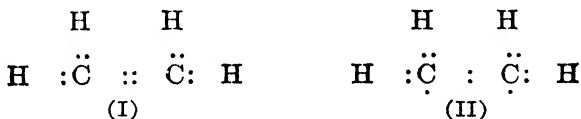
The new anhydrides which are formed are readily purified and constitute an interesting group of new compounds. The reaction between butadiene and maleic anhydride has been used as a quantitative method of analysis for butadiene in the presence of monoolefins.

Conjugated Partial Valences. There are other unsaturated acids which are of theoretical interest because the study of their addition reactions has brought to light new facts and interpreta-

¹ Consult Marek and Hahn, Catalytic Oxidation of Organic Compounds in the Vapor Phase, Chem. Cat. Co. (1932).

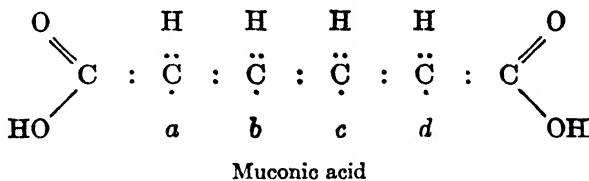
On the basis of this picturization, it is entirely reasonable to expect addition to take place at positions 1 and 4.² What is represented in the formula as the neutralized partial valences between 2 and 3 (dotted lines) becomes, after two hydrogen atoms are added, an ordinary double bond with residual valences. According to this conception a conjugated system represents a less degree of unsaturated than if there were two pairs of double bonds unaffected by each other. In the case of muconic acid there are only two un-neutralized residual valences, instead of four which would be present if the double bonds were not "conjugated."

According to Lewis the idea of partial valences can be pictured most satisfactorily in terms of electron structures as indicated in the following figures.



In figure (I), the double bond is represented analogous to the representation used in ordinary formulas. In figure (II), two electrons which constituted part of the double bond are completely separated, and represent the extreme case of free valences or unpaired electrons. Any intermediate stage in which these electrons are somewhat but not wholly separated represents the condition of partial valence.

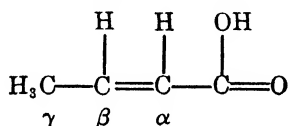
In the case of muconic acid we may similarly use a picturization of the extreme case.



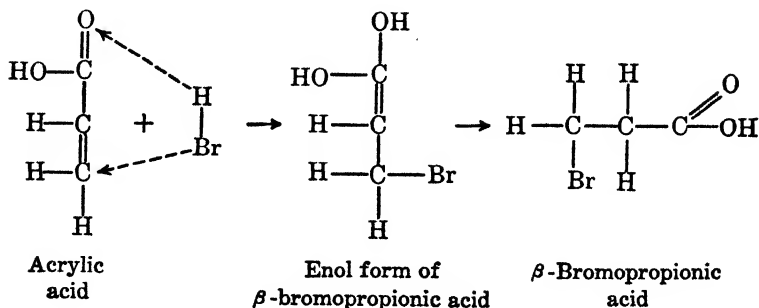
² Addition does not always take place in these positions; in other words the central positions 2 and 3 are not completely inactive, and addition sometimes takes place in the 1, 2 or 3, 4 positions. With some of the simpler dienes there is evidence that 1, 2 addition of HBr takes place first and then under the influence of both HBr and peroxides rearrangement may take place to give a final 1, 4 addition product. Thiele's theory merely seeks to explain why addition could and probably does take place on the 1, 4 positions in many conjugated diolefins.

Electron *b* not only has a tendency to pair with electron *a* but also with electron *c*. Similarly electron *c* can pair not only with *d* but also with *b*. Electrons *b* and *c* because of their ability to pair with each other have more opportunities to pair off than electrons *a* and *d*. Since unpaired electrons lead to addition reactions it is not surprising that addition to muconic acid takes place preferentially at *a* and *d*. This tendency of *b* and *c* to pair corresponds to what is represented by Thiele by a dotted line joining the two carbon atoms.

Conjugated systems may include double bonds between other than carbon atoms. A double bond between carbon and oxygen bears some resemblance to an olefin double bond and hence may be a part of a conjugated system as exemplified below.

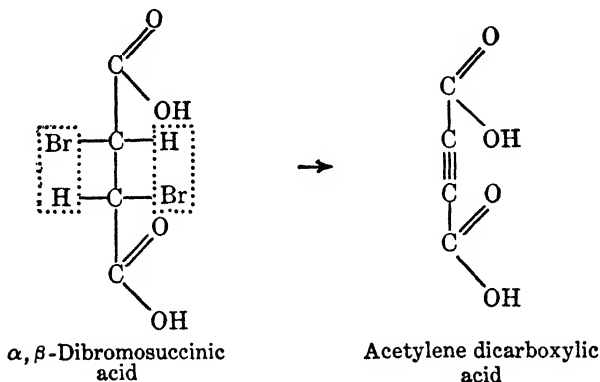


It has been found that acids similar to the one formulated above, in which, however, the double bond is between the β and γ carbon atoms, change over upon heating with alkalis into acids in which the double bonds are in the position shown above. The conjugated system is the more stable one, and as in the case of muconic acid, represents a lower degree of unsaturation than if the double bonds were not conjugated. The seemingly anomalous addition reactions of α -unsaturated acids (and other α -unsaturated carbonyl compounds) can be explained by a 1, 4 addition mechanism.



Other Unsaturated Acids. From the large number of unsaturated acids that are known, we have singled out for discus-

sion only a few of the more interesting ones. In addition to the acids with one or more double bonds in their structures, there are acids which have triply bonded carbon atoms in their formulas. Aside from linolic and linlenic acids which have been mentioned in connection with linseed oil, perhaps the only other unsaturated acid which need be mentioned is *acetylene dicarboxylic acid* which is formed by heating dibromosuccinic acid with caustic potash.



It should be noted that this method of preparation is exactly analogous to one of the methods of preparation of acetylene (p. 58). Acetylene dicarboxylic acid may also be prepared by the dehydrochlorination of chlorofumaric (*trans*) and chloromaleic (*cis*) acids. The former acid is dehydrochlorinated about

UNSATURATED ACIDS

	Melting Point	Bolling Point	K _a
Acrylic acid (propenoic acid), $\text{CH}_2=\text{CHCOOH}$..	12°	142°	5.6×10^{-5}
Crotonic acid (<i>trans</i> -buten-2-oic acid), $\text{CH}_3\text{CH}=\text{CHCOOH}$	72°	189°	2.15×10^{-5}
Isocrotonic acid (<i>cis</i> -buten-2-oic acid), $\text{CH}_3\text{CH}=\text{CHCOOH}$	15°	172°	3.6×10^{-5}
α Methacrylic acid (methyl propenoic acid), $\text{CH}_2=\text{C}(\text{CH}_3)\text{COOH}$	16°	(dec.) 163°	
Vinyl acetic acid (buten-3-oic acid), $\text{CH}_2=\text{CH}-\text{CH}_2\text{COOH}$	-39°	163°	3.8×10^{-5}
Oleic acid, $\text{CH}_3(\text{CH}_2)_7\text{CH}=\text{CH}(\text{CH}_2)_7\text{COOH}$	14°	286 100 mm.	
Linoleic acid, $\text{CH}_3(\text{CH}_2)_4\text{CH}=\text{CHCH}_2\text{CH}=\text{CH}(\text{CH}_2)_7\text{COOH}$	-11°	230 16 mm.	

48 times more readily than the latter.³ It is also interesting that the unsaturated carbon atoms, as usual, cause an increase in acidity so that this acetylenic acid is very strong, being comparable in strength with sulfuric acid.

PROBLEMS

1. Would you expect *cis-trans* isomerism to exist among the compounds having triple bonds instead of double bonds, in their structures?

2. Work out the structural formulas for all the monocarboxylic unsaturated acids having one double bond and four or less carbon atoms. Is there a possibility of geometrical isomerism in any of these cases?

3. Can α , β -dibromosuccinic acid exist in stereoisomeric forms? How many?

4. Three di-iodoethylenes are known. How might their structures be represented?

5. If fumaric acid is allowed to add on bromine at the double bond, will the resulting product be optically active? Can it be resolved into optically active compounds?

6. How do the statements "organic acids are weak" and "formic acid is the strongest organic acid" have to be altered in order to convey the truth?

7. Aconitic acid, $C_6H_6O_6$, which occurs naturally, can be made simply by heating citric acid. What is its structural formula?

8. What prediction can be made regarding the basic properties of a compound with the structure $R-N=CH_2$?

9. Utilizing the idea of conjugated partial valences picture the addition of H_2O to acrolein.

10. Write equations representing the mercuration of *cis* and *trans* butene-2. Why would it be anticipated that the *cis* isomer mercurates more readily than the *trans* isomer?

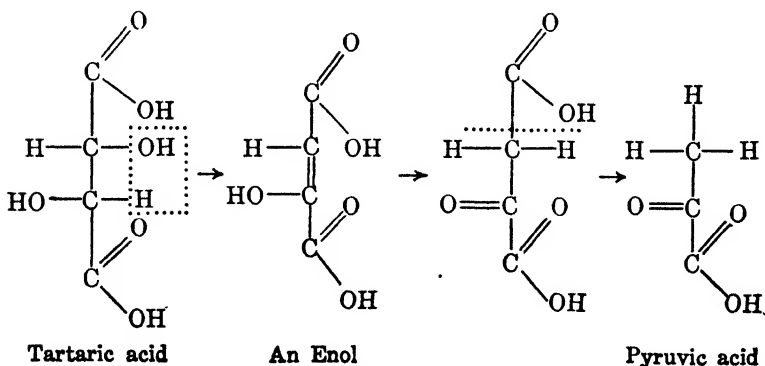
³ There are numerous other examples of differences in reactivity between *cis* and *trans* isomers. For example, *cis* butene-2 mercurates more readily with mercuric acetate than *trans* butene-2 while one isomer of 3-chloro-2-propen-1-ol dehydrochlorinates more readily to form propargyl alcohol than does the other isomer.

CHAPTER XIX

KETONIC ACIDS

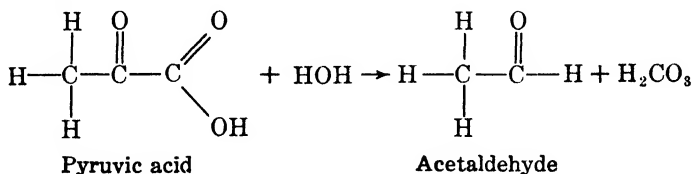
The simplest ketonic acid is **pyruvic acid**, $\text{CH}_3\text{COCO}_2\text{H}$. It is a liquid which boils at about 165° with decomposition. It is soluble, as would be expected, in water, alcohol, and ether, and has an odor resembling acetic acid. It may be prepared by the hydrolysis of α,α -dichloropropionic acid or by the mild oxidation of lactic acid, and both methods of formation indicate that it has the structure given above. It has acid properties much stronger than propionic acid and like other ketones is able to form a crystalline addition product with sodium bisulfite, and an addition product with hydrocyanic acid. It also forms reaction products with hydroxylamine.

Pyruvic acid is also sometimes called *pyroracemic acid* because it is one of the products of the decomposition of racemic acid by heat. It can also be obtained by heating ordinary tartaric acid or glyceric acid until they decompose. The decomposition of tartaric acid to give pyruvic acid probably takes the following course.



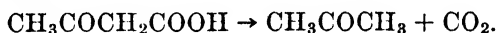
The reaction does not take place quantitatively in this way as various other products are formed at the same time.

When heated to about 150° with water, pyruvic acid hydrolyzes. This is in accordance with the fact that when non-metallic atoms are attached to adjoining carbon atoms they break apart easily (p. 111).



Pyruvic acid is an important compound biochemically as it is an intermediate in carbohydrate metabolism.

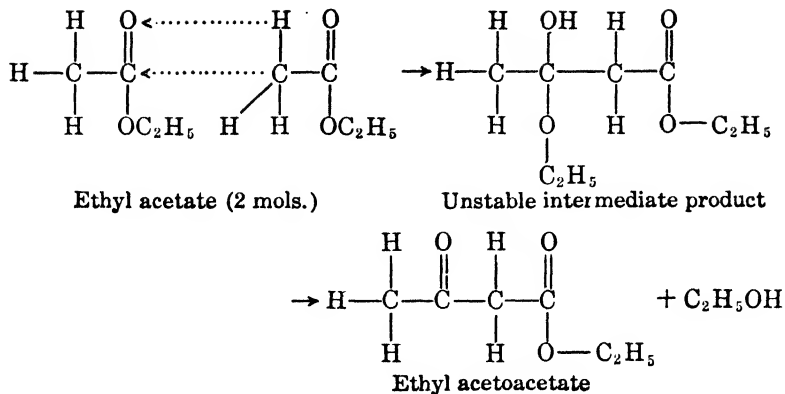
Acetoacetic acid, $\text{CH}_3\text{COCH}_2\text{COOH}$, is the only other ketonic acid which is of sufficient importance to merit individual discussion at this point. Its name is a contraction from *acetyl acetic acid* which correctly describes its structure. This acid occurs along with acetone and β -hydroxybutyric acid in the urine of diabetics and contributes to the acidosis which is present in severe cases. The acid itself can be obtained only in impure form as a syrup. It decomposes, when heated, into acetone and carbon dioxide.



It is probable that the reaction is really a hydrolysis in which acetone and carbonic acid are formed.

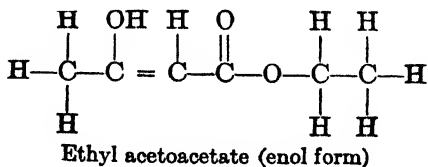
Ethyl acetoacetate (acetoacetic ester) is a highly important substance in organic chemistry because of its use in the synthesis of various organic compounds, and is of special importance from the historical standpoint. It is more important than acetoacetic acid itself, and is not prepared from it. It is commonly made by treating ethyl acetate (which contains some alcohol) with metallic sodium. Perhaps the simplest explanation of how the reaction occurs is that the sodium ethoxide which is formed causes the ethyl acetate to undergo condensation similar to the aldol condensation (p. 108) and thus plays the same role as is played by the alkali in the aldol condensation. This is called a Claisen¹ condensation.

¹ L. Claisen (1851-1936) was Professor of Chemistry at Kiel, Germany.



The condensation product first formed has a hydroxyl group and an ethoxyl group, $\text{C}_2\text{H}_5\text{O}$, attached to the same carbon atom and since such an arrangement is not very stable, alcohol separates and leaves the ethyl ester of acetoacetic acid. In the actual preparation of the substance the ethyl acetate is treated with a large quantity of sodium, which reacts with the ester and converts it into a sodium derivative which is to be discussed shortly. The ester itself is a colorless liquid, boiling point 181° , and has an agreeably fruity odor.

The structure of acetoacetic ester was a difficult problem to solve for the earlier organic chemists because it showed such diverse behavior toward different reagents. Its formula, as we have given it, indicates that the substance is a ketone, and the evidence for this structure seems conclusive, inasmuch as it reacts with sodium bisulfite, hydrocyanic acid, hydroxylamine and phenylhydrazine in the manner characteristic of ketones. It also may be reduced to the corresponding secondary alcohol. The acetoacetic ester, however, reacts with metallic sodium liberating hydrogen and shows unsaturated properties, both of which facts indicate that the ester has the structure of an unsaturated alcohol.

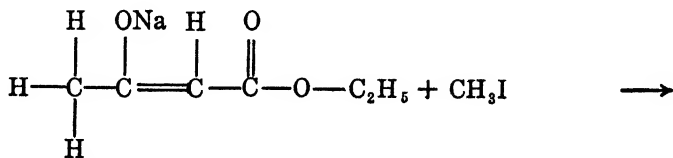


After the discussion concerning acetaldehyde (p. 109) the student will easily guess that the solution to the difficulty is to be found in the assumption of two tautomeric forms in equilibrium. This assumption makes it possible to explain how the substance may act as though it has both formulas. In fact, acetoacetic ester is a historic case in which tautomerism was shown to exist, and the evidence is more complete than in the case of acetaldehyde already cited.

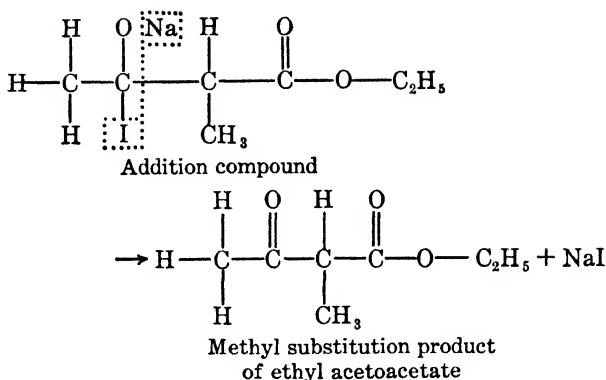
By cooling the ester to a low temperature, the ketone form separates as a crystalline substance (m.p. -39°), but the enol form does not freeze until a much lower temperature is reached, so that a separation of the two forms is possible. If the sodium compound of acetoacetic ester is treated at a low temperature with hydrogen chloride, the enol form of the ester is freed and can be recovered. The enol form shows distinct unsaturated properties; it adds on bromine rapidly, while the ketone form does not. If either the enol or the ketone form of the ester is allowed to stand at ordinary temperature it is converted gradually into an equilibrium mixture which constitutes the ester as it ordinarily exists, containing about 7 per cent enol form and 93 per cent ketone form. When tautomeric forms rearrange slowly so that a separation is possible, the phenomenon is spoken of as *desmotropy* and the tautomers as *desmotropic forms*.

Use of Acetoacetic Ester in Synthesis of Acids and Ketones

When sodium reacts with the ester it forms the sodium derivative with the formula $\text{CH}_3\text{C}(\text{ONa})=\text{CHCOOC}_2\text{H}_5$. When this compound is warmed with an alkyl halide, such as methyl iodide, an addition reaction probably first takes place, followed by a splitting off of sodium iodide.



Sodium derivative of ethyl acetoacetate

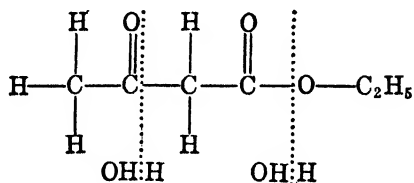


It will be recalled that hydroxyl and halogen will not remain attached to the same carbon atom. Similarly if the hydrogen of the hydroxyl is substituted by a metal, the metal halide splits off. The methyl substitution product of the ester pictured above exists in two tautomeric forms and will react with sodium as does the original ester. This sodium derivative can add on an alkyl halide again in the same manner and the sodium halide will split off again. By this means it is possible to substitute any one or any two alkyl groups for the two hydrogen atoms which are attached to the carbon atom between the two carbonyl groups in the original ester.

This result would not be of importance were it not for the fact that the acetoacetic ester and its derivatives can be decomposed in such a way as to give a variety of products. Acetoacetic ester, like other esters, is capable of being hydrolyzed into the alcohol and acid from which it is derived. As has already been stated, acetoacetic acid is itself quite unstable, and hydrolyzes to give acetone and carbonic acid. This happens readily in the presence of a dilute alkali with the formation of an alkali carbonate. No one would care to use acetoacetic ester, however, as a material for preparing acetone because it is too difficult to prepare and acetone is too easily made in other ways. However, if a substituted acetoacetic ester, such as, for example, $\text{CH}_3\text{COC}(\text{CH}_3)(\text{C}_2\text{H}_5)\text{COOC}_2\text{H}_5$, is heated with dilute alkali, the ester undergoes ordinary hydrolysis as usual and in addition

the *substituted* acetoacetic acid undergoes hydrolysis into a complex ketone and carbonic acid, analogous to acetoacetic acid itself. By this means it is possible to make a large number of ketones starting with acetoacetic ester. This manner of hydrolyzing the ester and its derivatives is sometimes spoken of as **ketonic hydrolysis**.

If the acetoacetic ester is boiled with a strong solution of potassium hydroxide, the ordinary hydrolysis of the ester takes place and in addition, a reversal of the Claisen condensation takes place in that the molecule splits in the same position where the union took place in its formation.

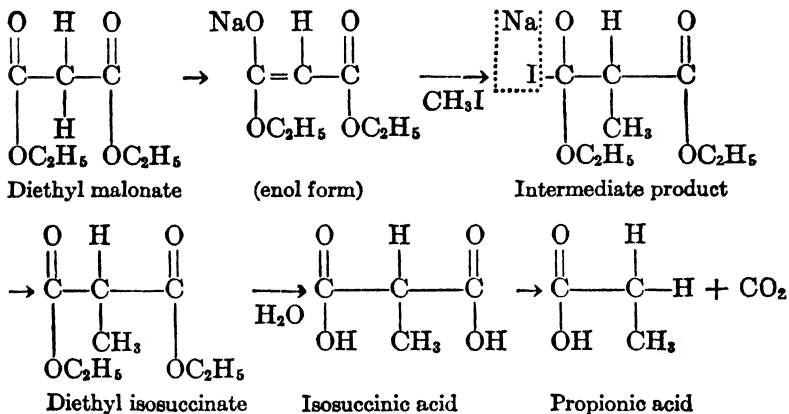


Ethyl acetoacetate (acid hydrolysis)

In this case the products formed are two molecules of acetic acid (which are of course neutralized by the base) and a molecule of ethyl alcohol. The substituted esters hydrolyze in the same way, which is sometimes spoken of as **acid hydrolysis**, not because acid is used in causing hydrolysis but because it is produced by the reaction. By hydrolyzing substituted acetoacetic esters in this way, practically any substituted acetic acid may be made regardless of its complexity, provided that the appropriate alkyl halides are available to prepare the particular ester which is to be decomposed.

Acetoacetic ester is not the only ester which can be used in this manner for synthetic work, but it is the most important reagent of the kind. Next in importance is **diethyl malonate**, $\text{C}_2\text{H}_5\text{OOCCH}_2\text{COOC}_2\text{H}_5$. This is not the ester of a ketonic acid but will be considered here because of its close relationship to acetoacetic ester. In this compound there is, as in the case of acetoacetic ester, a methylene group, CH_2 , situated between two carbonyl groups. Whenever this arrangement exists the hydrogen atoms of the methylene group migrate readily to one of the carbonyl groups, to form an enol form, which may react with

sodium. In the case of malonic ester the sodium derivative formed can add on alkyl halides and the products formed by this means may be hydrolyzed to produce dibasic acids. Acids which have two carboxyl groups attached to the same carbon atom easily lose carbon dioxide on heating to form monocarboxylic acids (p. 250). The use of malonic ester is illustrated below.



It is to be noted that by the use of malonic ester the same complex acids may be prepared as by the use of acetoacetic ester. From these acids, of course, many derivatives may be made. From the ketones, obtainable by use of acetoacetic ester, it is rather a simple matter to obtain secondary alcohols by reduction.

While syntheses by means of these esters are of historical importance they are by no means as important laboratory reagents as they once were. This is largely due to the growing use of the Grignard reagents for the preparation of the same compounds (p. 152). Both diethyl malonate and acetoacetic ester are, however, of considerable importance technically, as they are used for the manufacture of numerous dyes and synthetic drugs.

PROBLEMS

1. Is the formation of the ketone or the enol form of acetoacetic ester favored by making its solution alkaline? Why?
2. Indicate how isobutyric acid can be made starting with diethyl malonate.

3. Work out the steps in the synthesis of diethyl malonate, starting with chloroacetic acid.

4. Construct the formulas for methyl *s*-butyl ketone and 3,4-dimethyl-2-pentanone. Indicate how each can be prepared both from acetoacetic ester and by using a Grignard synthesis.

5. Taking into consideration the enolization of acetone itself, show how by reactions parallel to those used in acetoacetic ester synthesis, how methyl propyl ketone could be prepared from acetone. (Such syntheses can be accomplished. NaNH_2 is allowed to react with acetone to yield its sodium derivative.)

6. Taking into consideration how higher aldehydes undergo aldol condensation (p. 108), how would you expect the ethyl ester of propionic acid to condense in the presence of sodium ethylate?

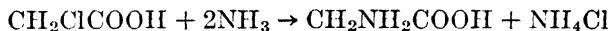
7. Why could not acetoacetic acid itself be used as a reagent instead of the ester? Would there be any reason for expecting it to act differently from the ester when it was treated with metallic sodium and with methyl iodide?

CHAPTER XX

AMINO ACIDS, PROTEINS AND RELATED SUBSTANCES

It is difficult to select any particular group of compounds as the most important from the standpoint of biochemistry. Different types of compounds are necessary and have their individual functions in the life processes of organisms. Of all the known compounds, however, none can be said to be more important in this connection than those which are at the same time amines and acids.

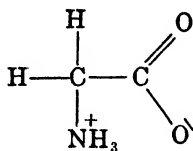
Glycine, glycoll or aminoacetic acid, $\text{CH}_2\text{NH}_2\text{COOH}$, is the simplest amino acid, and is typical of the class and hence will be used as an illustration in the discussion of the general properties of the amino acids. By reaction with nitrous acid it yields nitrogen gas and hydroxyacetic acid and from a consideration of the reactions of the primary amines with nitrous acid, it is apparent that the original acid has the structure indicated above. It can be prepared by the ammonolysis of monochloroacetic acid which is also evidence for this structure.



One of the most important characteristics of the amines is their basic property and their ability to form salts with acids. In aminoacetic acid, for example, we have an amino group that is capable of forming salts with acids, and along with it an acid group. The question naturally arises as to whether or not the acid group is able to react with the amino group.

If so, what are the results? When ammonia is brought in contact with water, it adds on hydrogen ions to some extent and leaves hydroxyl ions free in the solution. When ammonia comes in contact with an acid which furnishes a high concentration of hydrogen ions, a correspondingly high concentration of ammonium ions results leaving the negative ions from the acid free in solution. The essential thing about the interaction of ammonia and acids is the addition of the hydrogen ion by the ammonia. Since hydrogen ions are free to move independently in a solution they should be taken up by amino groups, no matter

where the amino groups are situated with respect to the acid group from which the hydrogen ions arise. If this should happen in the case of aminoacetic acid the product would have the following structure:

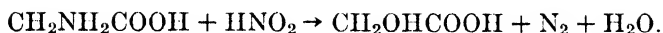


which might be described as an ionized internal salt. When the term "ionized" is used in this connection it must be understood in a qualified sense. Ions are free to move independently and in this case the positive and negative "ions" are attached to each other and cannot move independently. A structure of this kind is known as a *zwitterion* (German, "hybrid").

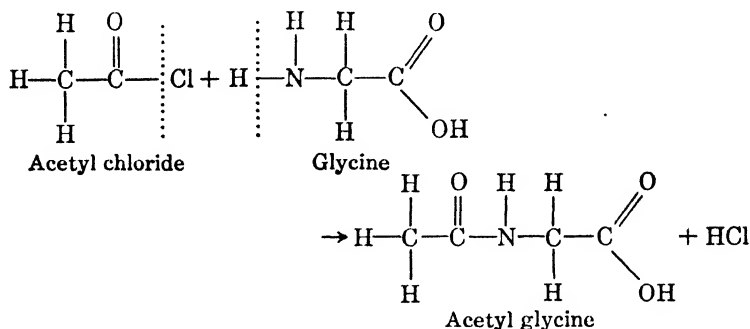
Aminoacetic acid in solution exists principally in the form of the internal salt as pictured above. It may be well to point out in this connection the fact that even salts formed by interaction of weak acids and weak bases, such as acetic acid and ammonium hydroxide, are not hydrolyzed to a high degree.

General Reactions of a Typical Amino Acid. Existing in solution, principally as salts of weak acids and weak bases, the amino acids are amphoteric and can form salts with strong acids or bases. Strong acids free the acid group of the amino acid while strong bases free the basic amino group. The salts formed, in both cases, are freely ionized in water solution and are soluble salts. Thus glycine is more soluble in acid or alkaline solutions than it is in pure water. In the sodium salt the organic ion is negative and in the hydrochloric acid salt the organic ion is positive.

In common with other amines, acid-amines (or internal salts) react with nitrous acid to produce nitrogen gas and the corresponding alcohol (alcohol-acid). In fact, when an amino group is in the α position with respect to a carboxyl group, the reaction with nitrous acid takes place more easily than in the case of the ordinary amines or ammonia itself. This reaction is used in determining and studying α -amino acids.

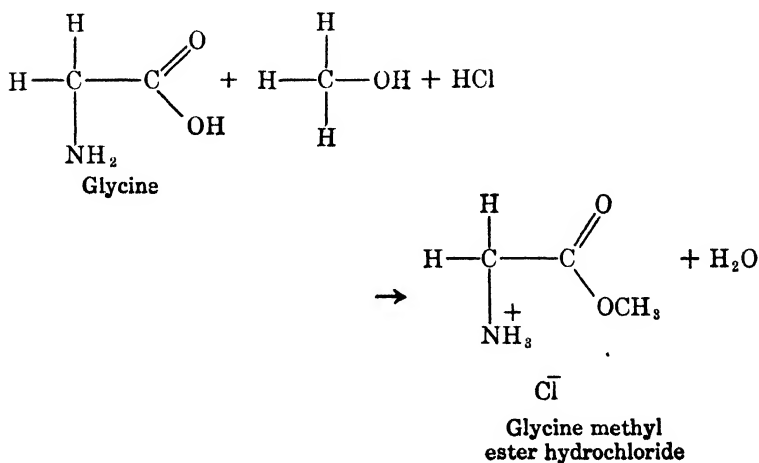


The amino acids react with acid chlorides and simple acid anhydrides, as do amines or ammonia.



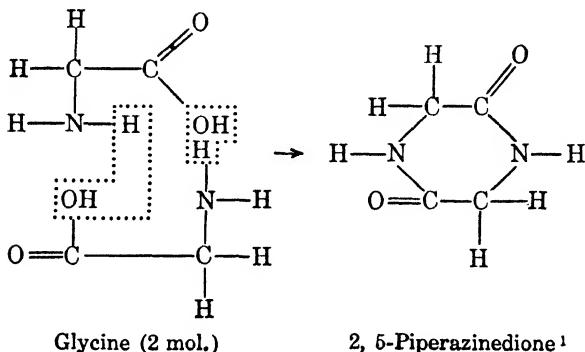
The substance formed in the case illustrated is a substituted acid amide, the formation of which is parallel to the formation of acetamide from acetyl chloride and ammonia.

The amine acids, because of the acid group, are able to form esters. Esters of amino acids are usually prepared by dissolving the amino acid in alcohol and introducing dry hydrogen chloride gas, which acts both as a dehydrating agent and as a catalyst. By this means the hydrochloride of the ester is obtained from the mixture, for the ester itself is basic in water solution.



From this ester hydrochloride the free ester itself may be obtained, by careful neutralization and subsequent purification. The amino acids, like other acids, form derivatives such as acid chlorides, amides, etc.

The α -amino acids may undergo inter-molecular condensation like the following.



This substance is a cyclic di-amide and may undergo hydrolysis to form the original amino acid. It is analogous to the cyclic diester formed from glycolic acid (p. 257).

Amino Acids from Proteins. The great importance of the amino acids lies in the fact that they are the chief products obtained by the hydrolysis of proteins. The proteins themselves are complex substances which may be shown, by several methods, to have very high molecular weights. The study of substances with high molecular weight always involves breaking down the complex molecules into simpler ones. Various methods of treating proteins in order to reduce them to simpler substances have been tried, but by far the most fruitful method is that of hydrolysis which is accomplished by long boiling with moderately concentrated acid or alkali, or by the use of enzyme preparations of animal or vegetable origin. Hydrolysis or diges-

¹ This particular ring of carbon and nitrogen atoms is called the *piperazine* ring. There are numerous types of rings; many have specific names. See other examples, p. 308. The name of this compound indicates the presence of two carbonyl groups in the 2 and 5 positions numbering from the nitrogen.

tion of proteins takes place in the digestive tract through the agency of enzymes. By each of these methods of hastening the reaction with water (hydrolysis), practically the same products are obtained.

The proteins (s. *prō'tē-in*) are divided into two large divisions, the *simple* and the *conjugated* proteins. The simple proteins produce on hydrolysis almost entirely α -amino acids, while the conjugated proteins produce not only α -amino acids but also other substances which are different for different kinds of conjugated proteins. Egg albumin is probably the most familiar simple protein. It yields practically nothing but amino acids on hydrolysis though, as a matter of fact, there is a little material, of carbohydrate nature formed at the same time. Casein from milk is a commonly known protein, belonging to the class of conjugated proteins. In addition to amino acids it yields phosphoric acid which in the original protein is linked to serine and possibly other amino acids, containing hydroxyl groups.

The amino acids which are formed by the hydrolysis of simple proteins in general include the following:

Monoamino monocarboxylic acids:

- (1) Glycine, amino acetic acid, $\text{CH}_2\text{NH}_2\text{COOH}$,
- (2) Alanine, α -amino propionic acid, $\text{CH}_3\text{CHNH}_2\text{COOH}$,
- (3) Serine, β -hydroxy- α -amino propionic acid $\text{CH}_2\text{OH-CHNH}_2\text{COOH}$,
- (4) Threonine, α -amino- β -hydroxy butyric acid $\text{CH}_3\text{-CHOHCHNH}_2\text{COOH}$,
- (5) Cysteine (*sīs'tēn*). β -thio- α -amino propionic acid, $\text{CH}_2\text{SHCHNH}_2\text{COOH}$,
- (6) Cystine, di- β -thio- α -amino propionic acid, $\text{COOH-CHNH}_2\text{CH}_2\text{SSCH}_2\text{CHNH}_2\text{COOH}$,²
- (7) Methionine, α -amino, γ -methylmercapto butyric acid, $\text{CH}_2(\text{SCH}_3)\text{CH}_2\text{CHNH}_2\text{COOH}$,
- (8) α -Amino butyric acid, $\text{CH}_3\text{CH}_2\text{CHNH}_2\text{COOH}$,
- (9) Valine, α -amino isovaleric acid, $(\text{CH}_3)_2\text{CHCHNH}_2\text{-COOH}$,

² This is really a diamino-dicarboxylic acid.

- (10) α -Amino valeric acid, $\text{CH}_3\text{CH}_2\text{CH}_2\text{CHNH}_2\text{COOH}$,
- (11) Leucine, α -amino isocaproic acid, $(\text{CH}_3)_2\text{CHCH}_2\text{CHNH}_2\text{COOH}$,
- (12) Isoleucine, α -amino- β -methyl valeric acid, $\text{CH}_3\text{CH}_2\text{CH}(\text{CH}_3)\text{CHNH}_2\text{COOH}$,
- (13) Norleucine (caprine), α -amino normal caproic acid, $\text{CH}_3(\text{CH}_2)_3\text{CHNH}_2\text{COOH}$,
- (14) Phenyl alanine, β -phenyl- α -amino propionic acid, $\text{C}_6\text{H}_5\text{CH}_2\text{CHNH}_2\text{COOH}$,
- (15) Tyrosine, β -para hydroxy phenyl- α -amino propionic acid, $\text{HOC}_6\text{H}_4\text{CH}_2\text{CHNH}_2\text{COOH}$.

Monoamino dicarboxylic acids:

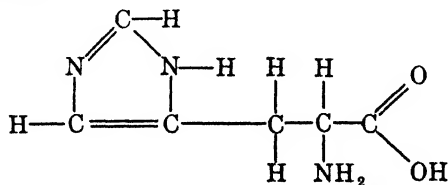
- (16) Aspartic acid, amino succinic acid, $\text{COOHCH}_2\text{CHNH}_2\text{COOH}$,
- (17) Glutamic acid, α -amino glutaric acid, $\text{COOHCH}_2\text{CH}_2\text{CHNH}_2\text{COOH}$.

Diamino monocarboxylic acids:

- (18) Arginine, α -amino- δ -guanidine valeric acid, $\text{NH}_2\text{C}(:\text{NH})\text{NHCH}_2\text{CH}_2\text{CH}_2\text{CHNH}_2\text{COOH}$,
- (19) Lysine, α,ϵ -diamino caproic acid, $\text{NH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CHNH}_2\text{COOH}$.

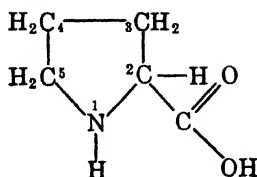
Acids containing heterocyclic ³ ring structures:

- (20) Histidine



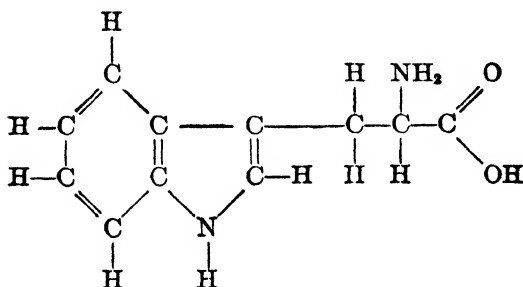
- (21) Proline, 2-pyrrolidine carboxylic acid,

³ Ring structures containing more than one kind of atom in the ring.

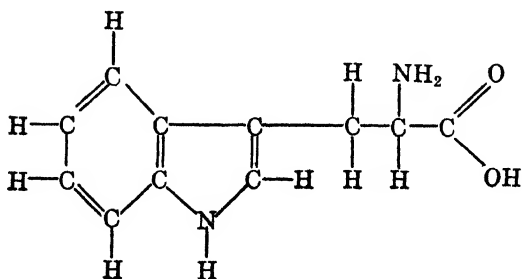


(22) Hydroxyproline, same as above with one hydroxyl group substituted for one hydrogen atom in the 4 position.

(23) Tryptophane, β -indole- α -amino propionic acid.



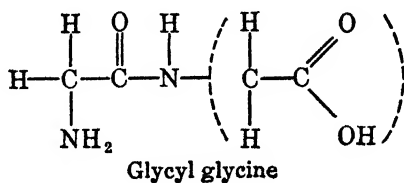
Three other amino acids have been reported to be obtained from casein, a conjugated protein : dihydroxy-diamino suberic acid, $C_8H_{16}N_2O_6$; diamino-trihydroxy dodecanoic acid, $C_{12}H_{26}N_2O_5$; and α -amino- β -hydroxy-glutaric acid, $COOHCH_2CHOHCHNH_2COOH$. From the thyroglobulin of the thyroid gland two iodized amino acids can be obtained, di-iodotyrosine and thyroxine. The former is a substitution product of tyrosine. Thyroxine which is commonly thought of as the active principle of the thyroid gland is more complex in structure as indicated below :



From these formulas it will be observed that all of these common amino acids have the amino group (or the NH group in 21 and 22) in the position α to the carboxyl group. This makes this particular carbon atom asymmetric except in the case of glycine, and hence there is a possibility of optical isomers. The amino acids as they are obtained from proteins by acid hydrolysis are optically active rather than racemic forms. If a protein hydrolysis is brought about by the use of an alkali as a catalyst, or if a protein is first treated with alkali and then hydrolyzed in an acid solution, the amino acids obtained in this way are mostly the inactive racemic forms. The treatment of a protein with alkali causes a racemization of the amino acids while they are yet a part of the large protein molecule.

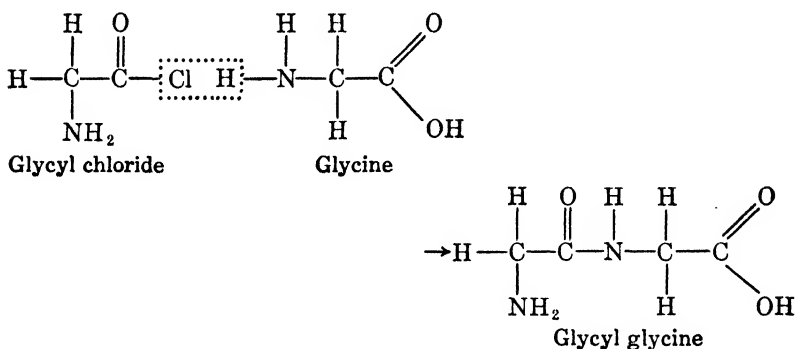
Linkage of Amino Acids in Simple Proteins. Since the same amino acids are obtained from proteins by several different methods of hydrolysis, it seems clear that the amino acid structures exist in the large protein molecules, in much the same form as they are found in the hydrolysis products. Of course, in the hydrolysis, water enters in, and the original protein molecules must be equivalent in composition to the sum of the molecules formed on hydrolysis, minus the water that actually reacts to form the amino acids.

The fact that the hydrolysis of a protein is slow, but is brought about by the presence of either acids or bases, calls to mind the esters and amides which behave similarly. There is very good evidence that ordinarily the amino acids of a simple protein are linked together through amino and carboxyl groups, and that the simple proteins are therefore substituted amides analogous to the one indicated in the formula below. In proteins a large number of amino acids are linked together in the manner indicated.



It will be noted in the formula given above, that if the group in dotted parentheses were replaced by a hydrogen atom the substance would be the simple amide of aminoacetic acid. The amide of aminoacetic acid on hydrolysis would yield aminoacetic acid and ammonia. The more complex substituted amide formulated above should undergo hydrolysis in the same way to produce two molecules of aminoacetic acid.

The substance pictured above can be prepared by making the acid chloride of aminoacetic acid, and treating this with aminoacetic acid itself.



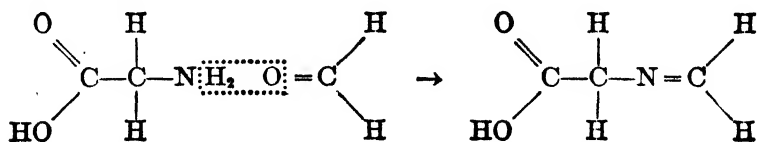
The glycyl glycine (a dipeptide) may then be converted into an acid chloride in the same manner and again treated with glycine or some other amino acid to give a still more complex molecule (tripeptide). Glycine has, as a matter of fact, been used more than any other amino acid for syntheses of this kind because it is relatively cheap (relatively easy to prepare). Emil Fischer,⁴ in whose laboratory much of the early work of this kind was done, synthesized by these methods substances with as many as eighteen amino acid residues linked together. The substances prepared in this way undergo hydrolysis much as do the proteins and there is good reason to believe that the simple proteins are substances just of this kind, except that they are more complex.

⁴ Emil Fischer (1852-1919) was perhaps the most eminent organic chemist of his time. His very extensive work was principally in the fields of the chemistry of proteins, carbohydrates and tannic acids. He was a professor in the University of Berlin.

A molecule of the "simplest" typical protein yields not less than about 250 amino acid molecules, representing perhaps 10 or 12 different *kinds* of amino acids. The evidence on which this statement is based will be given later. Recently (1947) Woodward has reported the synthesis by an ingenious method of very high molecular weight polypeptide molecules having a structure like fibrous proteins.

Further evidence that the proteins are made up in this way is shown by the way in which proteins and their hydrolysis products react with nitrous acid. When proteins are treated with nitrous acid in such a manner that the nitrogen gas evolved can be collected and measured,⁵ one obtains from .1 gram sample of protein a small amount of nitrogen gas (perhaps 1 cc.). This means that there is very little free amino nitrogen in the protein molecules. If the same protein is boiled with acid it will be found after a half hour that there is very appreciable increase in the nitrogen gas obtainable from the same amount of protein. This amount increases as the hydrolysis proceeds until it reaches a maximum of perhaps 25 cc. of nitrogen from .1 gram of the original protein. It is obvious that as the hydrolysis proceeds free amino groups are formed.

In a similar manner it can be shown that during hydrolysis of a protein, free carboxyl groups are formed. The amino acids in general cannot be titrated; the simple monoamino monocarboxylic acids, for example, are practically neutral due to the presence of both acidic and basic groups and their mutual neutralization. However, these and other amino acids can be titrated if they are first treated with formaldehyde. The treatment of glycine with formaldehyde may produce a methylene derivative in the following manner.



⁵ The most convenient form of apparatus for this purpose is that designed by D. D. Van Slyke (1883-), member of the Rockefeller Institute for Medical Research, New York.

After this treatment the acid can be titrated with alkali in the usual way as the group formed by the action of formaldehyde is not basic. Proteins react with formaldehyde in the same way, but even after treatment they are able to neutralize only a small amount of alkali, which shows the absence of many carboxyl groups. However, if the protein is partially hydrolyzed, for instance by enzyme action, and then treated with formaldehyde and titrated, it is able to neutralize more alkali. As hydrolysis proceeds the digest is able to neutralize more and more alkali after treatment with formaldehyde, until a maximum is reached. This corresponds to the complete hydrolysis of the protein. The method of titration after treatment with formaldehyde is known as *Sorenson's formal titration*.⁶

Thus there is very strong evidence that as the hydrolysis of a protein proceeds both carboxyl and amino groups are formed simultaneously. This can hardly be accounted for in any other way than that in proteins the common linkage is the one previously indicated.

Occurrence of Proteins. The proteins are of very great importance as they are constituents of all living animal and plant cells. The number of individual proteins which exist is probably an unthinkable number, because as a rule each species of plant or animal has its own characteristic proteins, and in one species alone there may be a large number of proteins characteristic of that species. The enormous number of proteins is entirely possible from the structural standpoint. Even if all proteins had the same composition, that is, if they all contained the same amino acids in exactly the same proportion and the same number per molecule, there would still be a very large number of different orders in which these same amino acids could be joined together and each would represent a different substance. As a matter of fact the number of kinds of amino acids in proteins vary from two or three, as in some of the protamines, up to 20 or possibly more. The molecular weights of the proteins may vary through a wide range so that the number of possible simple proteins is

⁶ S. P. L. Sorenson (1868-1938) was Director of the Carlsberg Laboratory, Copenhagen, Denmark.

stupendous. The many different kinds of conjugated proteins extend the limit of the number of possible proteins still further.

AMINO ACIDS FROM PROTEINS

	Gliadin (Wheat)	Zein (Maize)	Egg Albumin	Gelatin	Casein	Hemo- globin	Salmin ⁷
Glycine (per cent)	0.02	—	—	25.5	0.45	—	—
Alanine	2.00	9.79	2.22	8.7	1.85	4.2	—
Serine	0.13	1.02	?	0.4	0.5	0.6	7.8
Cystine	0.45	?	?	—	0.07	0.3	—
Valine	0.21	1.88	2.50	—	7.95	—	4.3
Leucine	5.61	19.55	10.71	7.1	9.7	29.0	—
Phenyl Alanine	2.35	6.55	5.07	1.4	3.88	4.2	—
Tyrosine	1.20	3.55	1.77	—	4.5	4.63	—
Aspartic Acid	0.58	1.71	2.20	3.4	1.77	4.4	—
Glutamic Acid	42.98	26.17	9.10	5.8	21.77	1.7	—
Arginine	3.16	1.55	4.91	8.2	3.81	5.4	87.4
Lysine	—	—	3.76	5.9	7.62	4.3	—
Histidine	0.61	0.43	1.71	0.9	2.59	11.0	—
Proline	7.06	9.04	3.56	9.5	7.63	2.3	11.0
Tryptophane	Pres.	—	—	—	1.5	2.61	—

ELEMENTARY COMPOSITION OF PROTEINS

	Carbon (per cent)	Hydrogen	Nitrogen	Sulfur	Iron	Phos- phorus	Oxygen
Gliadin (Wheat)	52.72	6.86	17.66	1.027			21.733
Zein (Maize)	55.23	7.26	16.13	0.600			20.78
Egg Albumin	52.75	7.10	15.51	1.616			23.024
Gelatin	49.38	6.80	17.97	0.700			25.13
Casein	53.13	7.06	15.78	0.800		0.86	22.37
Hemoglobin	54.64	7.09	17.38	0.390	0.335		20.165
Salmin	47.0	8.9	30.2				13.7

Determination of "Protein." Kjeldahl Method.⁸ When it is desired to determine the amount of protein in a sample of a foodstuff, for example, the usual procedure is to determine the total nitrogen that is present in the sample in the form of derivatives of ammonia. Since different proteins contain roughly the same percentage of nitrogen, the percentage of nitrogen found is

⁷ Comparatively a very simple protein, obtained from salmon sperm, mol. wt. about 750. It is one of a class of proteins known as *protamines*.

⁸ J. Kjeldahl (1849-1900) was a Danish chemist, Director of the Carlsberg Laboratory in Copenhagen.

multiplied by a factor, fixed by experience, to ascertain the amount of protein actually present. This method is satisfactory for the determination of the total protein in a sample, provided there is no nitrogen present aside from that in proteins. Since there is generally some nitrogen present in other forms, the figures obtained in this way are only approximations but are nevertheless useful for comparative purposes.

The total nitrogen (exclusive of nitrates, nitrites, etc., which are not present in proteins) is determined by destroying the protein with boiling concentrated sulfuric acid. After the digestion is complete the solution is diluted, and made alkaline. The ammonia is then distilled off quantitatively into a standard acid, and determined quantitatively by back titration. From the amount of ammonia obtained the amount of nitrogen and "protein" is calculated. Since proteins often are about .16 nitrogen, the percentage of nitrogen found may be multiplied by the reciprocal of this quantity, 6.25, to obtain a figure for the percentage of "protein" present.

Protein Molecules. Proteins even in relatively highly concentrated solutions have no appreciable effect on the freezing point of water. This means that their molecular weights are very high. Studies of the rate of settling of typical proteins under the influence of centrifugal force show that their molecular weights vary from about 15,000 up to perhaps 20,000,000.

The protein to receive most careful and systematic study to date is β lactoglobulin from milk (Brand). It has a molecular weight of 42,000, contains the various amino acid residues as follows: 8 glycine, 29 alanine, 21 valine, 50 leucine, 27 isoleucine, 15 proline, 9 phenyl alanine, 4 cysteine, 4 cystine, 9 methionine, 4 tryptophane, 7 arginine, 4 histidine, 33 lysine, 36 aspartic acid, 24 glutamic acid, 32 glutamine, 20 serine, 21 threonine, 9 tyrosine. Its molecular formula is calculated to be (close approximation):



Oxyhemoglobin (a conjugated protein) from horse blood, contains 0.335 per cent iron. If, as we must assume, there is *at least* one atom of iron to each molecule of the protein, .335 per cent

of the weight of a whole gram molecule is not less than 56 grams (at. wt. Fe = 56). On this basis the minimum molecular weight would be 16,665.

Hemoglobin combines chemically with a definite and small amount of carbon monoxide gas to form what is apparently a definite compound known as carbon monoxide hemoglobin. One gram of the protein combines with 1.338 cc. of the gas measured at standard conditions. It is possible, on the assumption that hemoglobin and the carbon monoxide unite molecule for molecule, to calculate the molecular weight of the hemoglobin. It is only necessary to calculate the amount of hemoglobin necessary to combine with one mole (22.4 liters) of the gas. In this case it is 16,669 grams, and this value therefore, on the above assumption, represents the minimum molecular weight of hemoglobin.

Actually ordinary hemoglobins are thought to have molecular weights about four times the above values, and thus contain four atoms of iron per molecule.

The characteristics of colloidal solutions, as contrasted with "true" solutions, are dependent upon the fact that the particles or molecules, as the case may be, are larger in colloidal solutions, though there is no sharp dividing line. The boundary which exists between the particles and the "solvent" causes a colloidal (kōl'oid-āl) solution to show the *Tyndall effect*, that is, the path of a ray of light passing through such a solution becomes visible due to the scattering of light caused by the boundaries. Due in part to the large size of the particles a substance in colloidal solution *does not diffuse* through parchment paper or through animal membranes.

The most important characteristic of colloidal solutions as contrasted with the "true" solutions is the fact that the particles are large enough so that there are effective boundaries between the colloidal particles and the solvent, or in other words, the colloidal particles have surfaces, with accompanying *surface (or interfacial) tension effects*. The amount of surface presented by a substance which is in a very fine state of division is very large. A one-centimeter cube has a surface area of 6 square centimeters. It can readily be calculated that if a cubic centimeter of material were broken up into a large number of very

small cubes, each 5 $m\mu$ (5 millionths of a millimeter) on a side, the surface area of the same material would be equivalent to approximately two fair-sized city lots. These particles would be about the smallest that are visible with an ultramicroscope, but are by no means the smallest colloidal particles. Proteins in solution are very frequently too small to be seen with the ultramicroscope.

Adsorption. Perhaps the most important phenomena connected with surface tension shown by colloids is that of adsorption. All molecules have some attraction for other molecules whether they are of like or unlike kind. The molecules on a surface are not surrounded on all sides by other molecules of like kind and as a result they have attraction for molecules of other kinds which therefore adhere on the surface. All surfaces show adsorption in this way. The cubic centimeter of substance mentioned above will have a greater or lesser tendency to adsorb substances, depending upon its composition and that of the molecules to be adsorbed. While the substance is in the form of a large cube this adsorption will be negligible in amount compared with its power of adsorption when in the form of colloidal particles. In the case mentioned above the surface and hence the adsorptive power is magnified about one million times by bringing it into a state of fine subdivision. In many cases the adsorptive phenomena become appreciable only when the material is very finely divided.

The readiness with which proteins in colloidal solution adsorb other substances makes them very difficult to purify. It is not possible to be sure that proteins and other like substances are pure in the same sense that many ordinary chemicals are. For example, it is difficult to obtain proteins in a form such that they are free from variable quantities of inorganic constituents which will leave an ash when the protein is burned.

Coagulation. Many proteins are thrown out of solution by heating to temperatures below the boiling point of water. Egg albumin in solution is coagulated by heat in this way. It, as well as some other proteins, is also coagulated when treated with strong alcohol. The changes brought about by heat treatment

or treatment with alcohol are irreversible, inasmuch as the protein cannot be brought back into solution after coagulation. Some colloidal protein solutions are caused to precipitate by vigorous agitation of the solution. It will be seen from these facts that protein solutions are often unstable as compared with ordinary solutions. Some other colloidal solutions are also unstable in the same manner.

Isoelectric Points. Proteins like the amino acids are amphoteric. If they contain a large proportion of dicarboxylic acids in their structure, they are more acidic than basic, but if they contain a larger proportion of free amino groups they are basic in reaction. In a hydrochloric acid solution a protein is in the form of a salt which might be designated as a "protein chloride." This substance ionizes like other salts into protein and chloride ions. When the same protein is in alkaline solution it exists in the form of a "sodium proteinate," which gives rise to negative protein ions and positive sodium ions. Evidence for the presence of these different ions in acid and alkaline solutions is obtained when protein solutions are electrolyzed. In acid solutions the protein travels toward the negative electrode and in alkaline solutions the protein goes in the opposite direction. This phenomena is known as *cataphoresis*.

That point of acidity or hydrogen ion concentration at which a protein has as much tendency to travel to one electrode as the other is known as the "*isoelectric point*" of that particular protein. If a protein is naturally an acid protein (excess of carboxyl groups) it will exist in its pure water solution to a larger extent as hydrogen and proteinate ions than in the form of protein and hydroxide ions, and will therefore tend to travel more to the positive electrode. To bring it to the isoelectric point it would therefore be necessary to add, for example, a little hydrochloric acid which will convert part of the protein into protein hydrochloride and equalize the tendency of the protein to go in the two directions.

Precipitation. Proteins form what are probably insoluble salts when solutions containing ions of heavy metals, or ions of acids of high molecular weight, are brought in contact with them.

In alkaline solutions proteins are mostly in the form of negative proteinate ions, and it is under these conditions that they form salts of heavy metals (positive ions) with especial ease. In acid solutions, on the other hand, the proteins are in the form of positive protein ions and under these conditions they form insoluble phosphotungstates, phosphomolybdates, tannates, pierates, etc., with especial ease. In the case of the precipitation by metallic salts, it has been found that the precipitating power of the different ions depends on at least two factors, first the atomic weight of the ion and second the number of positive charges carried by the ion. The higher the weight of the ion and the larger the number of charges carried, the more efficient is the precipitant.

The tanning of leather, as nearly as it can be described in a few words, consists of conversion of the proteins of the hide into insoluble salts of tannic acids, for example. If solutions of salts of heavy metals are applied to the prepared hides, a somewhat similar conversion into leather takes place.

The poisonous properties shown by all soluble salts of heavy metals and of acids such as phosphotungstic, etc., are due in part at least to their power of precipitating proteins and other colloids which are present in the cells of the body.

Color Reactions. The proteins give characteristic colors when treated with different reagents under definite conditions. These tests can be applied to identify proteins and in some cases give some idea of the nature of the protein. Some of the tests, for example, are given only by those proteins which contain certain types of amino acids. Only a few of the more important of the tests which are used in the studying of proteins will be mentioned.

Biuret Reaction. A protein in strongly alkaline solution when treated with a drop or two of very dilute copper sulfate solution gives a color which may vary from violet to pink. This color is not given by amino acids but is given by the intermediate hydrolysis products of the proteins, so that it may be used to determine when the hydrolysis of a protein is complete. The test is given by substances other than proteins, and in fact, gets

its name because the substance known as biuret, obtained by heating urea, gives the test.

Xanthoproteic Reaction. Proteins when treated with concentrated nitric acid solution turn yellow. When this material is treated with alkali it acts like an indicator and turns orange. This reaction is familiar to those who have allowed concentrated nitric acid to come in contact with the skin. The color is caused by the formation of nitro compounds and is given only by those proteins which have in their structure amino acids which are derivatives of benzene.

Aldehyde Reactions. When sulfuric acid is added to a protein solution containing a small amount of an aldehyde, so that it forms a separate layer in the bottom, a colored ring is formed at the junction of the two liquids which is more or less characteristic. This reaction may be applied in several ways and the color obtained is in general some shade of violet. The characteristic color is formed in this way only by proteins which contain the amino acid tryptophane.

Classification of the Proteins. The following classification of the proteins has been adopted by the American Society of Biological Chemists, and will give the student some idea of the different types of proteins that are known. The classification is not a scientific one based upon fundamental properties or constitution, but is to a certain extent convenient.

Simple Proteins

Yield only α -amino acids on hydrolysis.

- (a) Albumins. Soluble in pure water and coagulable by heat.
Egg albumin, lactalbumin.
- (b) Globulins. Insoluble in pure water but soluble in neutral solutions of salts. Coagulable by heat.
Serum globulin (blood serum), *edestin* (hemp seed).
- (c) Glutelins. Insoluble in all neutral solvents, but soluble in dilute acids and alkalis.
- (d) Prolamines. Alcohol soluble proteins. Soluble in 70-80 per cent alcohol, insoluble in water, absolute alcohol and other neutral solvents.

Gliadin from wheat, *zein* from corn, etc.

- (e) Albuminoids. Insoluble in all neutral solvents.

Collagen from tendons.

- (f) Histones. Not coagulable by heat, soluble in water and dilute acid; strongly basic and insoluble in ammonia.

Histone from thymus gland.

- (g) Protamines. Strongly basic, non-coagulable by heat, soluble in ammonia and yielding a large proportion of diamino acids on hydrolysis.

Salmin from salmon sperm.

Conjugated Proteins

Yield other substances in addition to amino acids, on hydrolysis.

- (a) Nucleoproteins. Prosthetic (additional) group is nucleic acid.

- (b) Glycoproteins. Prosthetic group contains carbohydrate.

Mucin from saliva.

- (c) Phosphoproteins. Prosthetic group contains phosphorus but is not nucleic acid or lecithin.

Casein from milk.

- (d) Hemoglobins. Prosthetic group is hematin or a similar substance.

Hemoglobin from blood. *Hemocyanin* from blood of invertebrates.

- (e) Lecithoproteins Prosthetic group is lecithin.

Derived Proteins

These are not natural proteins but are derived from them by the action of heat, reagents, etc.

Primary Derived Proteins

- (a) Proteins. First products of hydrolytic action. Insoluble in water.

- (b) Metaproteins. Products of further action. Soluble in weak acids and alkalis.
- (c) Coagulated proteins. Insoluble products formed by the action of heat or alcohol, etc.

Secondary Protein Derivatives

- (a) Proteoses. Soluble in water, not coagulable by heat. Precipitated by saturating their solution with ammonium sulfate.
- (b) Peptones. Soluble in water, not coagulable by heat, but *not* precipitated by saturating their solutions with ammonium sulfate.
- (c) Peptides.⁹ Two or more amino acids linked together through amino and carboxyl groups. May be synthesized.

Other Related Nitrogen Compounds

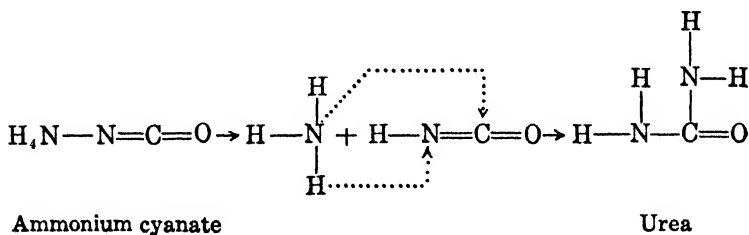
There are a number of nitrogenous substances which may well be discussed at this point although they are not amino acids nor are all of them closely related to the proteins chemically. Among these is urea, which is the final product in the metabolism of simple proteins, in the body. The proteins are taken into the body as food, are digested or hydrolyzed into amino acids and in the case of conjugated proteins, into other products as well. Except in growing individuals there is no continued accumulation of protein or other nitrogenous material, hence nitrogen must be continuously excreted in some form. If nitrogen were introduced into the blood in the form of ammonia it would cause serious disturbance, but in the form of urea it is

⁹ A naturally occurring peptide of considerable biological interest is *glutathione*. It yields on hydrolysis glutamic acid, cysteine and glycine and hence is tripeptide. It occurs very widely in tissues and may be involved in biological oxidations. It is a thioalcohol and is oxidized readily to the corresponding disulfide (p. 225) which is spoken of as oxidized glutathione.

not only harmless but acts as a diuretic in stimulating the action of the kidneys.

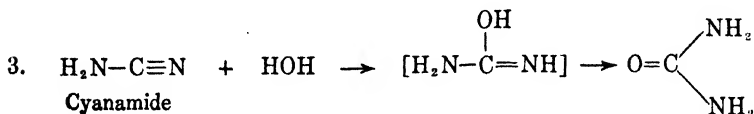
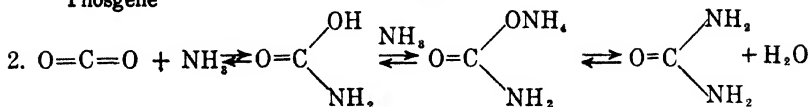
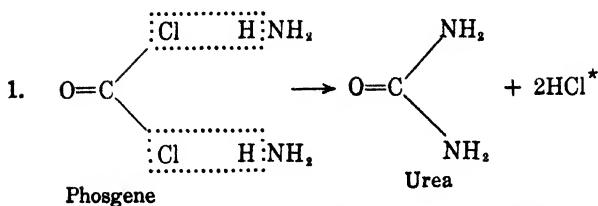
As has already been mentioned, urea is the di-amide of carbonic acid. It has the properties of a weak base and forms salts, of which the nitrate is best known, $\text{H}_2\text{NCONH}_3\text{NO}_3$. Urea is a di-base but on account of the weakening effect of the carbonyl group the secondary ionization is very weak and the salt of the di-base is hence unstable.

Its formation from ammonium cyanate is of historical importance because it was the first recognized "organic" substance to be made from materials which had an inanimate source. Wöhler¹⁰ in 1828 prepared urea from ammonium cyanate, which could be made in the laboratory independent of any organic source of material. Urea and ammonium cyanate are isomers and the change from one isomer to the other by the application of heat can be explained on the following basis. Ammonium salts dissociate upon heating and the ammonia formed in this case probably acts on the cyanic acid in a manner similar to that in which water acts on methyl isocyanate in the presence of alkali (p. 211), adding on at the double bond between carbon and nitrogen.

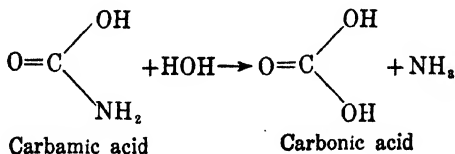
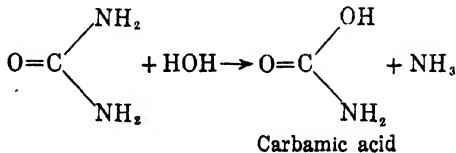


Urea may be made industrially by (1) the ammonolysis of phosgene (carbonyl chloride), (2) utilizing the reaction between carbon dioxide and ammonia and (3) the partial hydrolysis of cyanamide.

¹⁰ Friedrich Wöhler (1800-1882) was a German chemist, a close friend and co-worker with Liebig. He was Professor of Chemistry at Göttingen when he died.

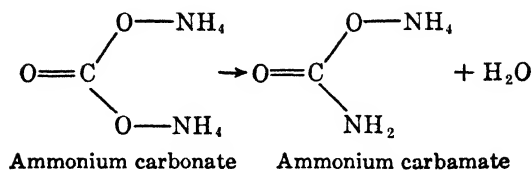


Urea, like other amides, may undergo hydrolysis. This takes place in two stages as there are two amide groups.

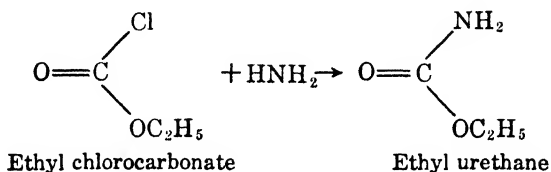


In each of these cases the acid formed may unite with the ammonia to form ammonium salts. The acid whose formula is indicated as both an acid and an amide is known as *carbamic acid*. Ammonium carbonate in the form of the commercial salt is partly *ammonium carbamate*, for ammonium carbonate is not very stable and one molecule of water is easily lost.

* See footnote, page 156.

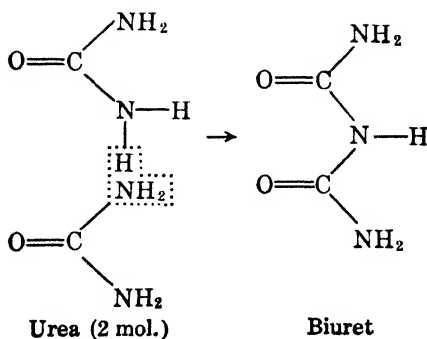


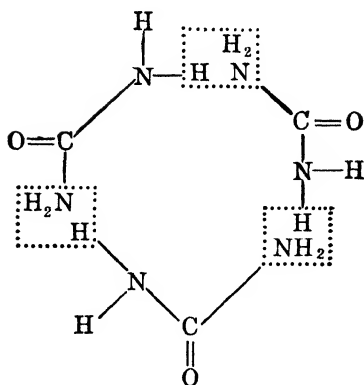
The esters of carbamic acid are known as *urethanes* and can be prepared by the action of ammonia on alkyl chlorocarbonates.



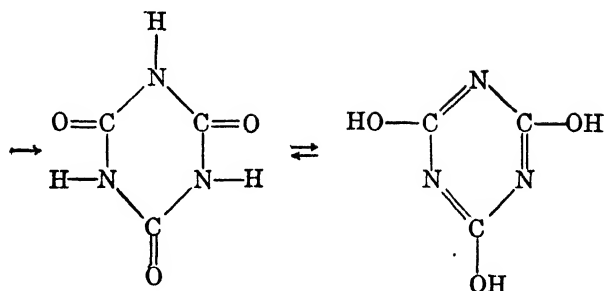
These substances have been used as sleep-producing drugs.

When urea is heated alone, ammonia is lost, and *biuret* (p. 319) or *cyanuric acid* (p. 210) (depending on the conditions) is formed as indicated.



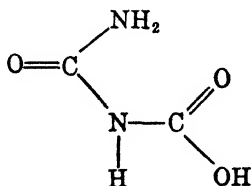


Urea (3 mol.)



Cyanuric acid (tautomeric forms)

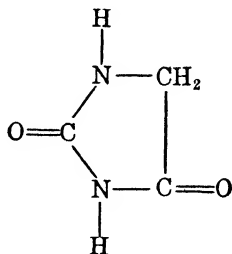
Urea finds its chief industrial use in the production of urea resins but it is also used as a fertilizer because of its high nitrogen content and nonacidic hydrolysis products. The *ureides* or acyl ureas have already been mentioned (p. 253). An important substance related to urea is *allophanic acid* which is



Allophanic acid

useful in identifying alcohols. The corresponding esters (allophanates) can be purified and studied. The free acid is unstable. Biuret is the amide of allophanic acid.

Hydantoins are cyclic urea derivatives of which the following is the simplest:

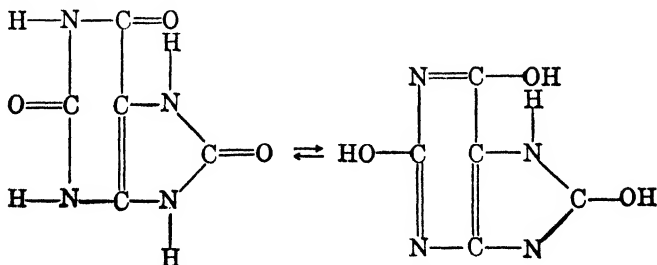


Hydantoin

It may be regarded as a cyclic mixed anhydride of carbamic acid and glycine and on complete hydrolysis yields carbon dioxide, ammonia and glycine.

The most important nitrogenous waste product of the body, aside from urea, is **uric acid**. This is formed in man chiefly from the nucleoproteins, and is excreted in the urine in small amounts. In birds and reptiles, however, uric acid is the chief end product of protein metabolism, in other words, nearly all of the nitrogen is eliminated in this form. The excrement of reptiles is said to be almost wholly the ammonium salts of uric acid.

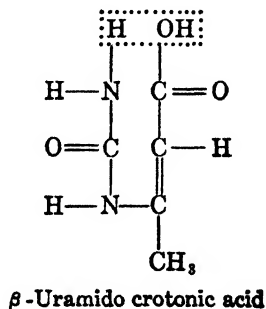
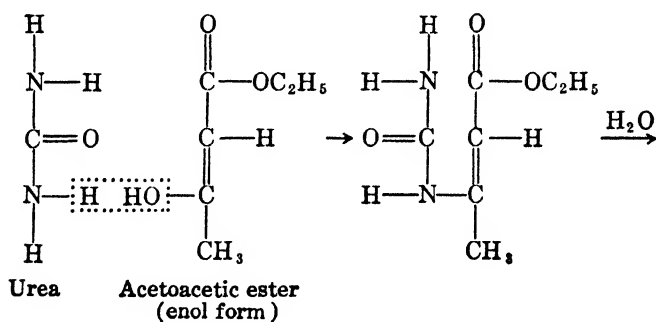
Uric acid like many of the more complex compounds exists in tautomeric forms. According to the evidence which in this case is quite definite uric acid has the following structures:

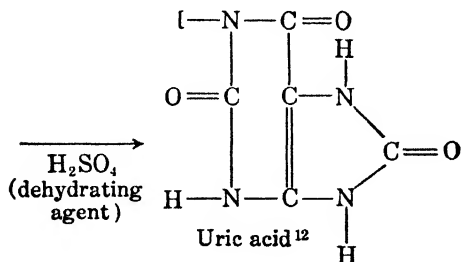
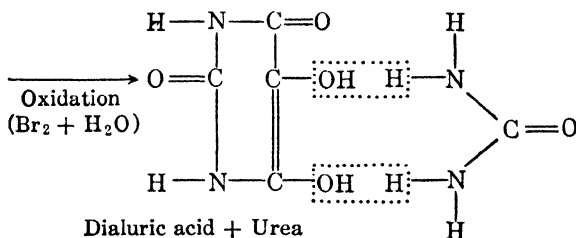
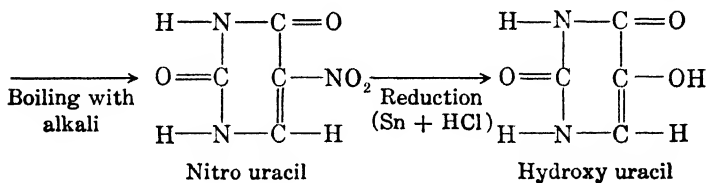
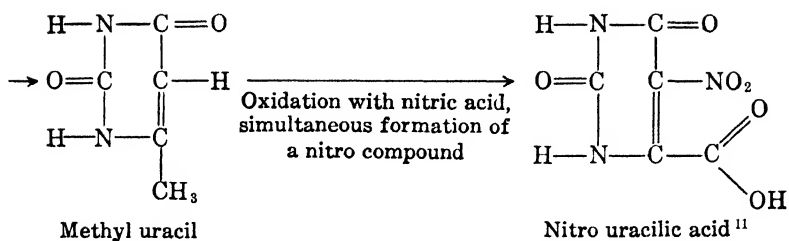


Uric acid (tautomeric forms)

The products of its oxidation as well as its method of synthesis are evidence for the first structure and the acid properties are in accord with the second formula. The first and more generally used formula is the ketone form; the second is the enol form.

The synthesis of uric acid has been brought about in several ways, and it is important that the student have some conception of how such a complicated substance can be built up from simple compounds. It should be noted that with more complicated substances we are less able to predict the exact course which reactions will take, and more often reactions take place which cause surprise. The modifying effect of several groups on each other, when they are all present in the same molecule, cannot be predicted accurately, and in the case of more complicated substances we have less experience to draw on and hence less basis for forming judgments. The following pictures the synthesis of uric acid as it was first carried out.



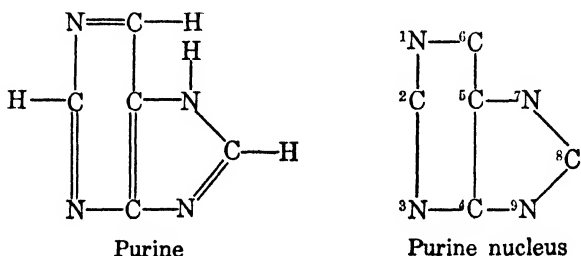


Purine Derivatives. Uric acid is not only derived from nucleoproteins in the body processes of man, but structures of similar nature are actually present in nucleoproteins. Uric acid and related substances are called *purines* and are derivatives of what for convenience is called the "parent substance" purine

¹¹ Amino uracil is also formed but cannot be used in the synthesis.

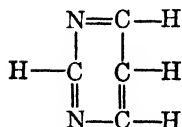
¹² Uric acid is the ureid of dialuric acid (see p. 253).

itself. As a matter of fact purine itself is of little importance compared with many of its derivatives, as it does not occur naturally. It has the structure indicated below. The purine nucleus (see below) is always numbered by common agreement in the manner indicated. This makes it possible to designate substituted purines by numbers which indicate the position of the substituents. If no substituent is designated for a given position, it is understood that enough hydrogen is present to fill the valence requirements.

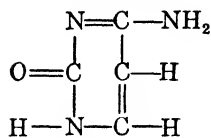
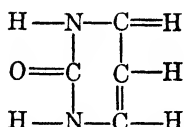


Uric acid may be called 2,6,8-trioxypurine. *Caffeine* (kăf'-ê-ën) which occurs in coffee beans and to a larger extent in tea leaves may be designated 2,6-dioxy-1,3,7-trimethylpurine. It is more often called 1,3,7-trimethyl xanthine (xanthine is 2,6-dioxypurine). *Theobromine* which is one of the active ingredients of cocoa and chocolate is 2,6-oxy-3,7-dimethylpurine but is more commonly called 3,7-dimethyl xanthine. *Adenine* (6-amino purine), *xanthine* (mentioned above) and *guanine* (2-amino-6-oxypurine) are products other than amino acids, which are obtained from nucleoproteins. They, in combination with a carbohydrate, *pyrimidine bases* and phosphoric acid, form what are called *nucleic acids*.

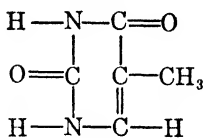
Pyrimidine Bases. Another related series of compounds known as the pyrimidines are formed by the careful hydrolysis of the nucleic acids which are obtained from nucleoproteins. Pyrimidine itself may be regarded as the parent substance and its structure as well as those of some of its important derivatives follow.



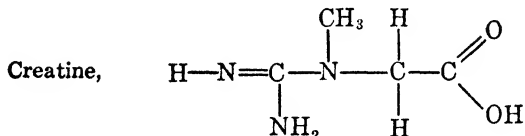
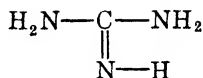
Pyrimidine

Cytosine
(may be obtained
from nucleic acid)

Uracil

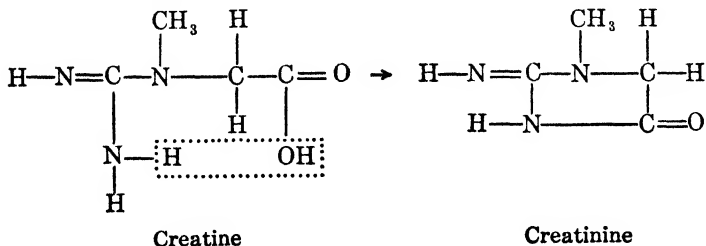
Thymine
(occurs combined
in nucleic acid)

Guanidine. This substance is closely related to urea, and is obtained by the oxidation of guanine. It is stronger in its base-forming properties than urea but weaker than ammonia. Its structure is represented by the formula:



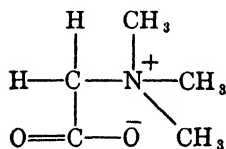
as is shown by the formula, is a substituted guanidine, or from another standpoint may be regarded as a substituted glycine. It is an important substance physiologically as it occurs to as high as .3 per cent in muscle and also in other tissues.

Creatinine is an anhydride of creatine from which it is formed in the body. It is a normal constituent of urine.



Asparagin occurs in asparagus as well as in many sprouting seeds, etc. It is the amide of aspartic acid and has the formula $\text{CONH}_2\text{CH}_2\text{CHNH}_2\text{COOH}$. It probably occurs as a "building stone" in proteins but is converted to aspartic acid and ammonia by hydrolysis. *Glutamine* is the corresponding amide of glutamic acid, $\text{CONH}_2\text{CH}_2\text{CH}_2\text{CHNH}_2\text{COOH}$.

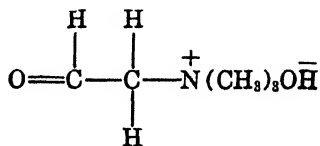
Betaine (bē'tā-ēn) occurs in beet roots and is present in large quantity in beet molasses. It also occurs in some seeds and in the flesh of fish as well as in other tissues. It has probably the structure of an inner salt, and since all the hydrogens attached to the nitrogen are replaced by other groups, it is one of the quaternary salts.



Betaine

The fact that betaine in its crystalline form has a molecule more of water in its composition than indicated above has led some to give betaine the structure of both an acid and a base. The water however can easily be accounted for as water of crystallization. Betaine hydrate when heated to about 100° loses a molecule of water and when heated to a higher temperature decomposes to form trimethylamine. This is analogous to the breaking up of tetramethyl ammonium iodide into methyl iodide and trimethylamine. The betaine which is present in beet molasses is a source for commercial trimethylamine. Substances which have structures similar to betaine itself are included in a more general class of *betaines*.

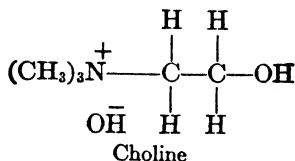
Muscarine is an aldehyde-base closely related to betaine.



Muscarine

It has been found in some species of poisonous mushrooms, and is itself a powerful poison. The poisonous properties may be ascribed to the presence of the aldehyde group as well as the substituted amino group which is common to many poisons.

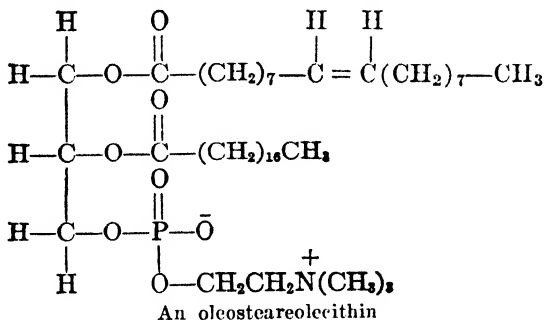
Choline is an important alcohol-base which is directly related to muscarine and betaine. Its formula is



It occurs in bile, in hops, mustard seeds, etc. Choline is a hydrolysis product of a group of complex glycerophosphoric esters known as *lecithins*.

Acetyl Choline $\text{CH}_3\text{COO}-\text{CH}_2\text{CH}_2\text{N}(\text{CH}_3)_3^+\text{OH}^-$ has recently been found to be of great importance from the standpoint of nerve physiology. It is present and brings about its effects in very low concentrations.

Lecithins occur as very important constituents of all tissues and are especially abundant in nerve tissue and egg yolk. The formula of an oleo steareo lecithin is indicated below.



This substance as its formula indicates is an ester of glycerol with fatty acids and phosphoric acid, an ester of choline and an inner salt, all combined in one molecule. It hydrolyzes as would be expected into glycerol, oleic acid, stearic acid, phosphoric acid,

and choline, and the hydrolysis products can be separately identified. Practically all natural occurring lecithins contain unsaturated groups in the fatty acids. Saturated lecithins can be obtained from the natural occurring lecithins by hydrogenation.

There are a number of substances related to the lecithins in which other bases than choline are present. These along with lecithins and other substances with similar solubilities and properties are classified together as *phosphatides*. The chemistry of the phosphatides has been very incompletely worked out. They are wax-like substances and are very difficult to purify. They frequently exist in colloidal solution.

Neurine is an unsaturated base closely related to muscarine and choline, with the formula $\text{CH}_2=\text{CHN}^+(\text{CH}_3)_3\text{OH}^-$. It is easily obtained from choline and is formed by the action of bacteria upon lecithins. It gets its name from the fact of its association with lecithin which occurs in nervous tissue. It is one of a number of nitrogenous bases which are sometimes called "ptomaines." When foods are acted on by bacteria, substances of this sort are eventually formed but by the time putrefaction has gone this far, the food is obviously unfit for consumption. Certain kinds of meat, fish, and vegetables are acted on by bacteria and may contain harmful bacterial toxins, or the bacteria themselves, without revealing their unfitness for food by odor or appearance. The bacterial toxins are highly potent and specific poisons, probably protein in nature.

Cadaverine is another nitrogenous base which gets this name because it was first isolated from a human cadaver, where it was formed by putrefaction. It is a diamine with the structure $\text{NH}_2(\text{CH}_2)_5\text{NH}_2$. There are a number of substances of this sort which are formed by bacterial action on proteins. Usually the individual amines formed are related to and are formed from certain particular amino acids. Some of the amines are poisonous or otherwise active physiologically, and some are nearly without effect.

Taurine, $\text{CH}_2\text{NH}_2\text{CH}_2\text{SO}_3\text{H}$, is an amino sulfonic acid. It is a hydrolysis product of *taurocholic acid*, a complex acid found principally in bile.

PROBLEMS

1. If 0.445 g. of a pure monoamino acid upon treatment with nitrous acid gives 112 cc. of nitrogen measured at standard conditions, what is the molecular weight of the acid?

2. How do you account for the fact that the amount of amino acids recovered from salmon is considerably more than 100 per cent of the weight of the original protein?

3. Starting with COCl_2 what reagent would be necessary to use to form ethyl chlorocarbonate?

4. By use of the Kjeldahl method of determining protein, and using the factor 6.25, what percentage protein would the following pure proteins appear to be: casein, egg albumin, gliadin?

5. Suppose it were possible to dehydrate urea like other amides (p. 201), what would be the product formed? (This may be accomplished by use of metallic sodium.)

6. Suppose that leucine is burned up in the body to produce urea, carbon dioxide and water. How many liters of carbon dioxide and how many grams of urea and water would be produced from 10 grams of the amino acid?

7. Construct the formulas for caffeine, theobromine, adenine and guanine.

8. What process is involved in the conversion of cysteine to cystine? How can a similar process result in the formation of a pentapeptide from a well-known tripeptide?

9. From the table of proteins given, select the one protein which you might expect to have the highest formol titration value.

10. Write the formula for the piperazine derived from alanine. Could it exist in optically active forms? How many?

11. The glycerophosphoric acid obtained by the partial hydrolysis of a "lecithin" is optically active. What does this tell regarding the structure of the lecithin?

12. When proteins are treated with alkali the asymmetric groups in them are racemized so that later hydrolysis by any available method yields racemic amino acids. Amino acids themselves do not racemize readily when treated with alkali. In terms of enolization picture what happens in these cases.

CHAPTER XXI

CARBOHYDRATES

There is a group of exceedingly important widely occurring substances which are composed of carbon, hydrogen and oxygen only, and in which the ratio of hydrogen to oxygen is usually the same as in water. An example of such substance is cane sugar which has the molecular formula $C_{12}H_{22}O_{11}$. The substance *from the standpoint of the molecular formula alone* might be considered as 12 atoms of carbon combined with 11 molecules of water. It would then be a "hydrate" of carbon, or a "carbohydrate." It was in this way that the name originated, though we do not regard the compounds as hydrates of carbon.

As a matter of fact there are some substances very closely related to the typical members of this class which do not have hydrogen and oxygen in the same ratio as in water, and yet it is convenient and customary to classify these substances as carbohydrates also. There are also some substances which we have already studied which as far as molecular formulas are concerned might be considered as "hydrates" of carbon, but are not classified as carbohydrates. Among these are formaldehyde, CH_2O , acetic acid, $C_2H_4O_2$, and lactic acid, $C_3H_6O_3$.

Simple Sugars—Monosaccharides

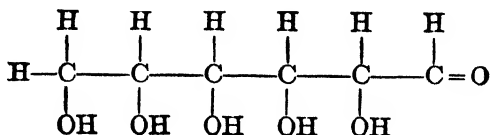
One method of classifying simple sugars is on the basis of the number of carbon atoms in the molecule. Because of their importance we shall confine our discussions of the simple sugars or *monosaccharides* almost entirely to the *hexoses* which have the molecular formula $C_6H_{12}O_6$, and the *pentoses* with the molecular formula $C_5H_{10}O_5$. The hexoses are decidedly the more important group of the two, though both types occur abundantly in nature. In addition to these two groups there are *heptoses*, $C_7H_{14}O_7$, *octoses*, $C_8H_{16}O_8$, *nonoses*, $C_9H_{18}O_9$, *tetroses*, $C_4H_8O_4$, *trioses*,

$C_3H_6O_3$, and a *biose*, $C_2H_4O_2$. These compounds are structurally related to the hexoses and pentoses but are, as a rule, synthetic products rather than naturally occurring sugars and therefore will not be treated in detail. Glycolic aldehyde, CH_2OHCHO , is the only biose. We shall see later that it is structurally closely related to some of the typical sugars.

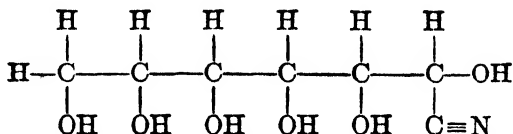
Glucose. One of the most important of all carbohydrates is a hexose sugar which is known by the different names: *glucose*, *dextrose*, *grape sugar*, *corn sugar*. It is the principal ingredient in glucose syrup which is used by bakers, confectioners and housewives. It is also sold in the powdered form and in the form of solid cakes. The color of the commercial products may range from almost white to distinct brown. (This should not be confused with ordinary brown sugar which is cane sugar not completely freed from molasses.)

The molecular formula for glucose as may be determined by the usual methods is $C_6H_{12}O_6$. The arrangement of the atoms in the molecule in the case of a substance of this complexity is not easy to determine, because there are so many possibilities. There are a few distinct chemical properties, however, which give us some clue as to what the arrangement must be like. For example, the fact that glucose cannot be broken down into substances with less carbon atoms to the molecule, by the action of water even in the presence of dilute acids, indicates that all six carbon atoms in the molecule must be attached to each other. Glucose can be made to react with acetic anhydride, to form a pentaacetyl derivative, or in other words, one molecule of glucose reacts with five molecules of acetic anhydride. This indicates that there are five hydroxyl groups in a glucose molecule. Knowing therefore that there are six carbon atoms attached to each other, and that there are five hydroxyl groups no two of which could be on the same carbon atom (as this would bring about instability), the problem of working out the structure becomes much simplified but is by no means solved. Since glucose is very easily oxidized and gives the silver mirror test readily, an aldehyde structure suggests itself, though the silver mirror test is not specific for aldehydes.

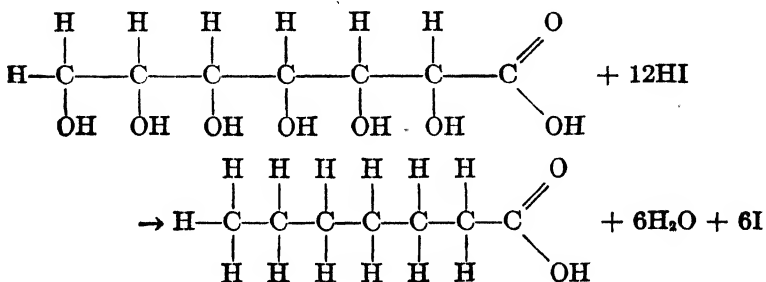
The following structure is the one that may be proposed tentatively.



There might be six carbon atoms all attached to each other in a branched chain but evidence presented below shows that glucose has a straight chain structure. Glucose reacts with hydrocyanic acid as do other aldehydes and ketones, forming a product which, if the above formula is correct, has the following structure,



That the substance formed from glucose has the structure indicated is shown by the fact that it can be hydrolyzed to give an acid (p. 202), and that upon reduction with hydriodic acid this acid becomes *normal* heptylic acid.



This reduction is in accordance with the general reaction by which alcohols may be reduced to hydrocarbons (p. 103). That the acid obtained in this way is *normal* heptylic acid can be shown by a synthesis of *normal* heptylic acid, and by proving the iden-

tity of the acid so obtained with the acid obtained from glucose. The identity of the acid obtained from glucose with *n*-heptylic acid proves the existence in glucose both of the aldehyde group and the straight chain. In accordance with the suggested structure, glucose reacts with phenylhydrazine, hydroxylamine, etc., like other aldehydes and ketones. The term *aldose* is applied to those sugars which, like glucose, are aldehydes in structure.

Before considering the structure of glucose further let us turn to the other sugars which are closely related to it.

Other Aldohexoses. The formula which has been proposed for glucose shows the presence of four asymmetric carbon atoms in the molecule. A number of space isomers of glucose should then be possible. These actually exist and with glucose are known as the *aldohexoses*. Like other naturally occurring products glucose itself is optically active and is not a racemic mixture of *d*- and *l*-forms. It is *dextrorotatory*, and from this it gets the name dextrose.

There are two space isomers of glucose which are known to occur in nature, namely, **galactose** and **mannose**. Galactose is formed along with glucose by the hydrolysis of a more complex carbohydrate—lactose or milk sugar, which makes up about four per cent of the weight of cow's milk. Galactose also occurs as a part of, and may be obtained by the hydrolysis of, other more complex carbohydrates. When a naturally occurring hexa-alcohol known as mannitol is carefully oxidized, mannose is produced. This substance is also formed by the hydrolysis of certain naturally occurring vegetable substances and is said to occur in the free state in orange peel. Both galactose and mannose undergo the same reactions that are mentioned for glucose and by exactly the same means it would be possible to show that their structure (disregarding spacial arrangement) is exactly the same as that of glucose. Neither of these substances is the optical antipode of glucose, and they are slightly different in physical and chemical properties. Both galactose and mannose are *dextro*-rotatory.

Aldopentoses. There are naturally occurring sugars which have formulas exactly like that of glucose except that there is one less secondary alcohol group (CHOH) in their structures.

These substances are known as aldopentoses. **Arabinose**, for example, is formed by the hydrolysis of a complex carbohydrate *gum arabic*, **xylose** is obtained by the hydrolysis of carbohydrates which are present in wood, straw, bran and like materials. **Ribose** is formed as one of the products of hydrolysis of vegetable nucleoproteins.

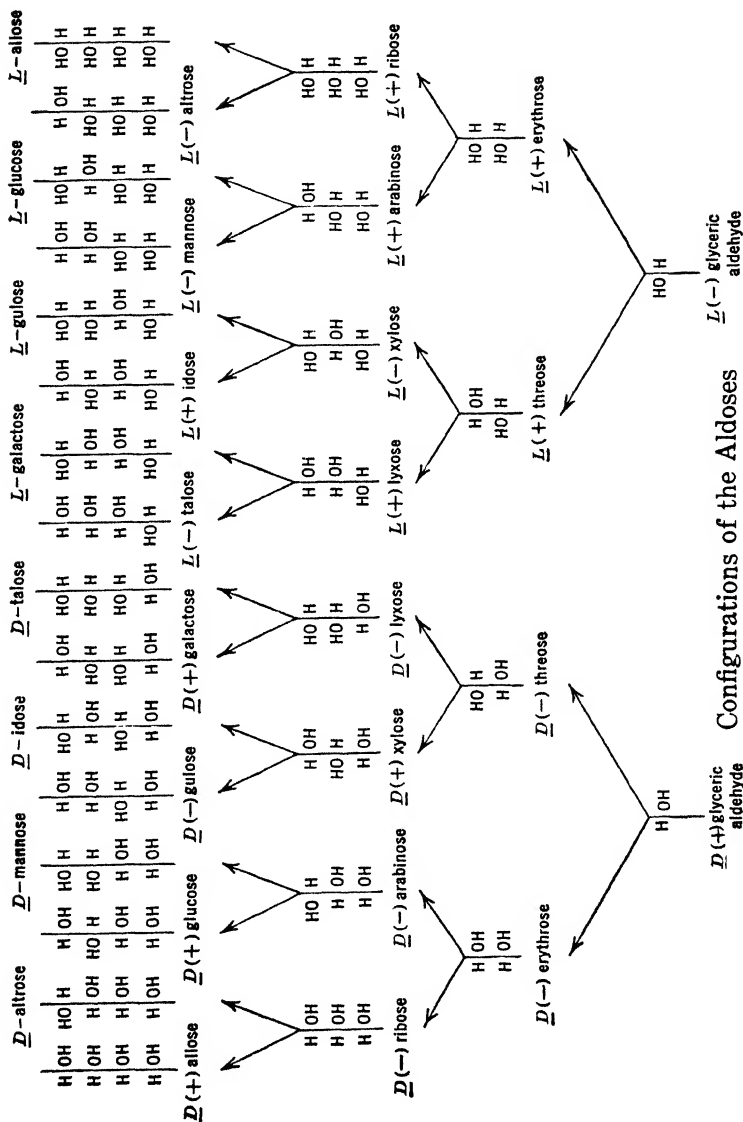
Rhamnose is one of those substances which it is convenient to classify with the carbohydrates which does not have hydrogen and oxygen in the ratio of two atoms of hydrogen to one of oxygen. It occurs in the form of complex derivatives in plants. It is a methyl pentose, $\text{CH}_3\text{CHOHCHOHCHOHCHOHCHO}$.

Configuration of the Aldoses. The problem of determining the stereochemical configurations of the simple sugars has been a very complex one. We shall take space only to indicate some of the conclusions of the study and the evidence on which we may base a decision as to the configurations of the common simple sugars. The spacial arrangements of the others have been determined and in many cases several lines of evidence, which we shall not take space to cite, lead inevitably to the same conclusions.

On page 341 is given a table showing in abbreviated form the structural relationships between the different aldoses. In each abbreviated formula the primary alcohol group (at the bottom) and the aldehyde group (at the top) have been omitted as well as the symbols for the asymmetric carbon atoms. It will be noted that there is a D^1 family and an L family of sugars. The choice as to which glyceric aldehyde configuration should be called D is purely an arbitrary one. The one so designated is assigned to the *dextrorotatory* form of glyceric aldehyde which then becomes a reference substance, to which all other substances are related. The " D " designation does not signify anything with regard to direction of rotation, but does indicate a stereochemical relationship to *dextrorotatory* glyceraldehyde. All members which have the lower hydroxyl group designated on the right are D sugars regardless of how they affect polarized light. Once this is decided all the other configurations fall in line with the decision.

It is actually possible experimentally to build up sugars on the basis of the scheme on p. 341. A lower sugar may add hydrocyanic acid at the aldehyde group. This forms a new asymmetric carbon atom, hence *two* stereoisomeric cyanide derivatives are formed simultaneously.

¹ The capital letters D and L are coming into use to designate families of compounds whereas the small letters d and l may be used to indicate direction of rotation in specific compounds. $D(-)$ means that a compound belongs to the D family but is *levorotatory*.



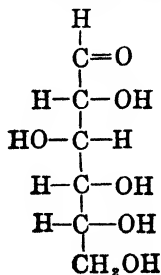
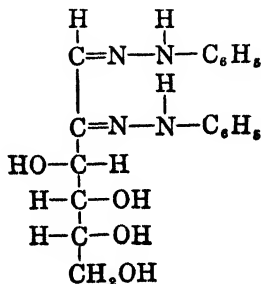
These can be hydrolyzed to acids, converted into lactones and reduced to aldehydes. There results two stereoisomeric higher aldoses (in accordance with the diagram) from each lower aldose.

How can we know that galactose (for example) has the configuration assigned to it in the chart? The answer in this case is comparatively simple. Galactose is the only aldose which experimentally yields on oxidation an *inactive* dicarboxylic acid (both aldehyde and primary alcohol group oxidized) and which also may be derived experimentally from a pentose which on oxidation yields an optically *active* dicarboxylic acid. Correspondingly there is only one pair of configurations among the aldohexoses for which this would be possible and these configurations may be assigned to the two (*D* and *L*) galactoses.

Having decided upon the galactose configuration (other evidence confirms this decision) we are able to assign the proper configuration to the pentose (lyxose) from which galactose may be derived by cyanohydrin synthesis. This, in turn, makes possible the assignment of the proper configuration to the pentose, arabinose, because arabinose experimentally yields on oxidation an optically *active* dicarboxylic acid, and in only one of the remaining cases would this be possible.

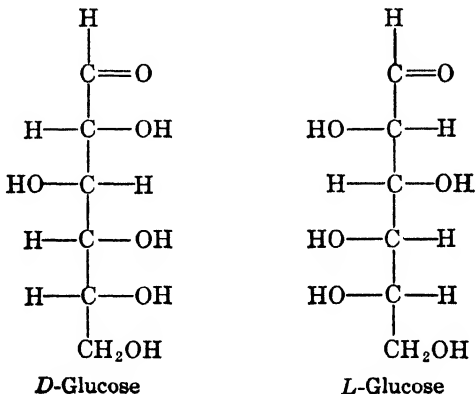
The third and fourth hexose formulas from the left therefore represent mannose and glucose because both of these sugars are obtained experimentally from arabinose. To decide which is which we can cite the experimental fact that when glucose is treated with HCN , the products hydrolyzed and oxidized to dicarboxylic acids, there is produced one optically *active* acid and one which is *inactive* by internal compensation. Mannose when treated in a similar manner yields two optically *active* acids. This shows that the third formula belongs to glucose while the fourth should be assigned to mannose.

A reaction which is useful in the study of sugars generally and also in the determination of configuration is that with phenylhydrazine. Phenylhydrazones are first formed but as outlined later (p. 465) the reaction proceeds further in the case of simple sugars producing a dihydrazone (osazone). The relationship between *D* glucose and its dihydrazone is indicated below.

*D*-Glucose*D*-Glucose dihydrazone

An inspection of the configuration on p. 341 will show that *D* glucose and *D*-mannose should produce the same dihydrazone and that the same should be true of *D*-galactose and *D*-talose, etc. These results are realized experimentally.

Configuration of D Glucose and Other D Sugars. In the previous sections are given the details whereby it is possible to ascribe to ordinary *D*² glucose one of the formulas indicated below. On the basis of convention chemists have agreed that when the formulas are written in this manner "D" sugars including *D*-glucose shall be represented with the lowest hydroxyl group on the right of the carbon atom. The antipode of glucose is then represented by the second formula.



Derivatives of these two antipodes must be assigned configurations which correspond to these spacial arrangements.

This nomenclature is likely to be confusing to the student unless clarified. If we start with a *dextrorotatory* substance like *D*-glucose, and convert it into some other optically active substance, there is no assurance whatever that we will obtain a *dextrorotatory* substance (p. 269). For example, *D*-glucose can be converted to an aldo-pentose by methods which need not be discussed here, but which do not involve a direct substitution on an asymmetric atom (p. 271) and the resulting pentose is a *levo*-

² See footnote p. 340.

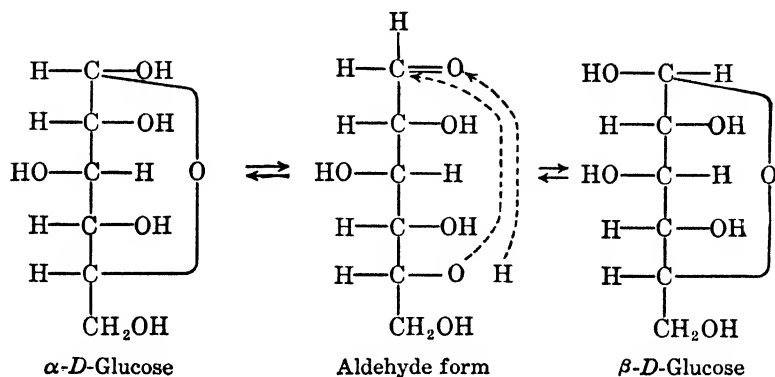
rotatory arabinose. Many other similar transformations lead to similar results. In this case the pentose formed is called *D*-arabinose, the name indicating the important fact that the substance is structurally related to *D*-glucose. *Dextrorotatory* arabinose likewise is structurally related to *L*-glucose and is called *L*-arabinose.

Mutarotation of Glucose. When ordinary glucose is dissolved in water its specific rotation (p. 265) is $+109.6^\circ$ but on standing this changes gradually for a number of hours until it reaches a constant value $+52.6^\circ$. This change takes place rapidly if the solution is made slightly alkaline. Some chemical change must be responsible for the great change in rotation. Yet glucose can be recovered from the solution in the original form.

The only acceptable explanation is that glucose exists in tautomeric forms which reach an equilibrium quite slowly in water solution. In fact, two forms of glucose have actually been prepared, at least in practically pure form. The ordinary form of the sugar is called α -*D*-glucose, and has the specific rotation given above; the other is called β -*D*-glucose, and has a specific rotation of $+20.5^\circ$. When either form is dissolved in water the same equilibrium mixture is formed upon standing.

α and β -*D*-Glucose. The structures of these two forms of glucose is now known with comparative certainty, and the first key to the solution lies in the fact that in dilute HCl solution glucose reacts with one (only) equivalent of methanol to yield a total of one equivalent of a mixture of two stereoisomeric methyl derivatives. The fact that it reacts with methanol at all under these conditions means that a hydroxyl group is present which is not an ordinary alcoholic group. That it reacts with only one equivalent means that this one hydroxyl group is different from the other four. That *two* optical isomeric derivatives are produced indicates that there is a *fifth* asymmetric carbon atom in the final products. The fact that the aldehyde properties of the glucose disappear during the reaction shows that the uppermost aldehyde carbon atom is involved. The whole matter clears up

if we assume that glucose with the structure already given has by virtue of its alcoholic properties added on to its own aldehyde group to form hemiacetals with the cyclic structures indicated.

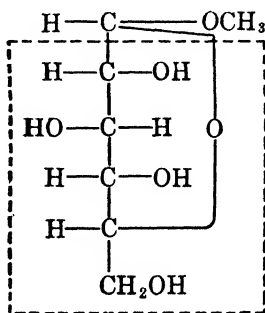
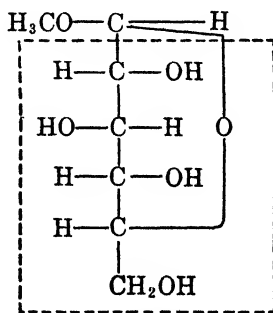


As we have already noted in the cases of succinic and glutaric acids and γ and δ hydroxy acids, the formation of rings by intramolecular reaction takes place with comparative ease, so that it should be expected that a substance with the aldehyde structure indicated above would undergo such a reaction. The *two* ring structures are inevitable since the number of asymmetric carbon atoms is increased from four to five; these structures are optical antipodes only insofar as the fifth (uppermost) asymmetric carbon atom is concerned. Such structures are sometimes spoken of as *epimers*.

These two forms of glucose which are in equilibrium in solution constitute the major part of the substance and can react with methanol to yield the mixture of the two corresponding derivatives. Only a very small amount of the aldehyde form is present but since the different forms are in equilibrium the whole of the glucose may act as an aldehyde (*e.g.*, by adding HCN, oxidizing to a carboxylic acid, reacting with phenylhydrazine, etc.) as indicated in the discussion of the configuration of the aldohexoses. α -D-glucose presumably changes to β -D-glucose by passing through the aldehyde form.

The question naturally arises whether the particular ring structures indicated are the ones present in glucose or whether the other alcohol groups may not react in a similar manner. This has been a matter of much dispute and experimentation. There is no question that other alcohol groups, particularly the third one from the aldehyde group, can react in a similar manner. The preponderance of evidence indicates, however, that the pyranose (6 membered ring) structures pictured above constitute the principal forms present in the equilibrium mixture and that other cyclic forms analogous to these constitute minor (but not necessarily unimportant) constituents. One of the principal lines of experimentation followed to settle a question of this sort involves complete methylation (page 172) of glucose in which case all five hydroxyl groups are involved, and then breaking down the molecule and determining which of carbon atoms holds no methoxyl group. This is evidently the carbon atom to which the oxygen of the ring was attached.

α and β -D-Methyl Glucosides. The two methyl derivatives of glucose which form directly by reaction with methanol evidently have the structures indicated below and are therefore *mixed* acetals inasmuch as the two groups attached through oxygen to the aldehyde carbon atom are different. Such derivatives are called *glucosides*. It is interesting to note that one of these forms has a high rotatory power $+157^\circ$ corresponding to α -D-glucose and the other has a low rotatory power corresponding to the other form.

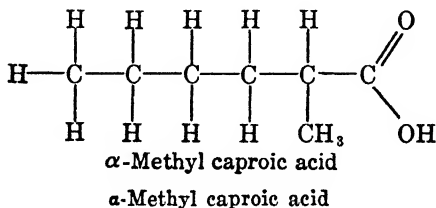
 α -D-Methyl glucoside β -D-Methyl glucoside

It will be noted that the part of the structures enclosed by dotted lines above are identical in the epimeric glucosides and also identical to the corresponding part of the two glucose structures. The differences

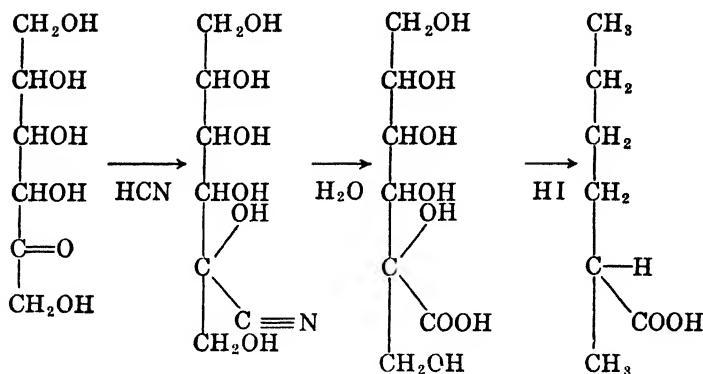
between the rotatory powers of the four structures must be due principally to differences in the asymmetry of the uppermost carbon atom. The molecular rotatory powers (page 270) of the two glucosides are 30,458(+157° × 194) and -6,401(-33° × 194) respectively. The mean molecular rotatory power is 12,028 which then represents the molecular rotatory power of that portion of the structure which is enclosed by dotted lines. The effect of one configuration (on the fifth asymmetric atom) is to raise this value by 18,430; the opposite configuration lowers this value by the same amount.

To show the validity of this method of calculating we may consider the two glucoses. Their molecular rotations are 19,728 and 3,690 respectively. The mean value (corresponding to the structure enclosed by dotted lines above) is 11,709 which checks within a few per cent of the value of the same structure calculated from the glucosides. The rotatory power of a compound with several asymmetric carbon atoms is *approximately* the summation of the effects of the individual parts of the whole structure, provided the rotatory powers are all measured under similar conditions.

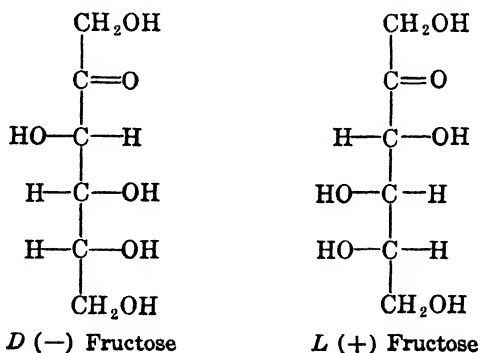
Keto-Hexoses. When cane sugar which has the molecular formula $C_{12}H_{22}O_{11}$ is hydrolyzed, there are formed equal quantities of *d*-glucose and another sugar which is known as "*levulose*" because it is strongly *levorotatory*. Levulose, which is also known as **fructose** or *fruit sugar*, has many properties in common with its isomer glucose; it is very easily oxidized, does not undergo hydrolysis, adds on hydrocyanic acid, reacts with phenylhydrazine, hydroxylamine, etc. When it is treated with hydrocyanic acid a nitrile is formed which may be converted to the corresponding acid. Reduction of this acid with hydriodic acid produces α -methyl caproic acid with the formula:



This reaction indicates that fructose has the structure of a ketone and that the acid is formed in the following manner.



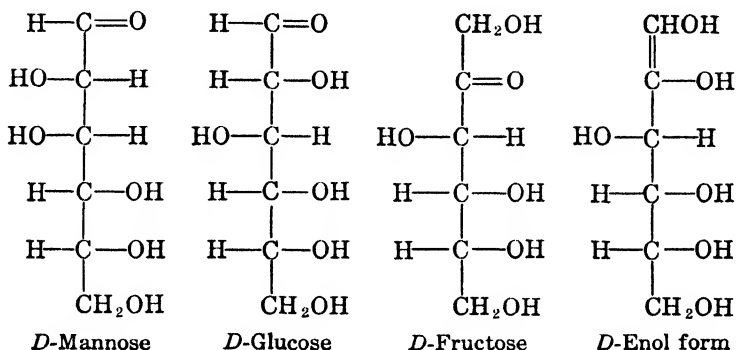
As fructose evidently contains the ketone group and six carbon atoms in its structure it is called a *keto-hexose*. Levulose or fructose is the only ketose that is at all important. There are three asymmetric carbon atoms in the molecule, and hence a possibility of eight stereoisomers. It happens, however, that the dihydrazone of fructose is identical with the one formed from *D*-glucose. From this fact alone the configurations of ordinary levulose or fructose and its antipode are determined to be as indicated below.



It is to be noted that the naturally occurring levulose (*D*-fructose) is strongly *levorotatory*, but is closely related structurally to *D*-glucose. The *dextrorotatory* form of fructose designated *L*-fructose is similarly related to *L*-glucose.

Like *D*-glucose, *D*-fructose is present in solution in cyclic forms. This fact will enter into our discussion of the structure of sucrose.

Equilibrium Between Different Hexoses—Enol Form. If a solution of *D*-fructose is allowed to stand in slightly alkaline solution for some time, it is partly converted into a *D*-glucose and *D*-mannose, and there is an equilibrium established. The same equilibrium is obtained if either of the other two sugars is allowed to stand in a weakly alkaline solution. This reversible change is explained on the basis of the formation of an enol form of these sugars.



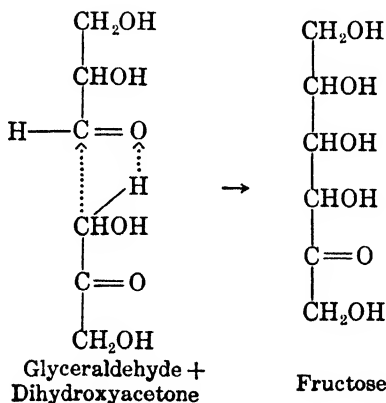
The enol form pictured is derived from each of the three isomers. By its formation the number of asymmetric carbon atoms is reduced (in the case of the aldoses) from four to three. The alkali would be expected to favor the conversion of any one of the sugars into the enol form (p. 110), and the reversal into the keto form (that in which the carbonyl group is present) may take place in such a way as to produce any of the three sugars. This phenomenon is interesting especially in view of the fact that *D*-glucose, *D*-fructose and *D*-mannose are three of the four important naturally occurring hexoses. It is probable that transformations like these occur in nature.

Synthesis of Naturally Occurring Simple Sugars. The synthesis of naturally occurring organic compounds has taken many strides forward since the synthesis of urea by Wöhler (p. 323) but no synthesis has aroused more interest than that of the naturally occurring sugars such as fructose and glucose. There are several methods by which monosaccharides can be built up but only a few will be mentioned.

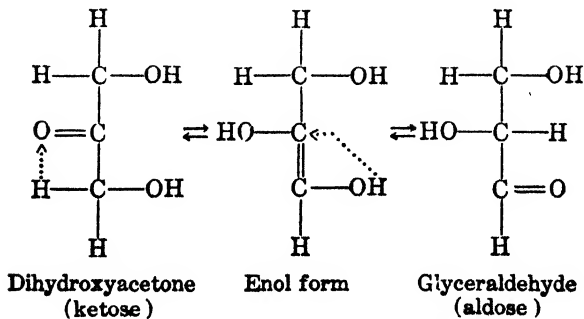
When formaldehyde is allowed to stand in lime water, a polymerization takes place and there is formed a sweet syrup which has the composition represented by the formula $\text{C}_6\text{H}_{12}\text{O}_6$, which was called *formose*.

As might be expected such a synthetic product does not consist of any single sugar, but is a very complex mixture of different sugars. It is optically inactive and is said not to be fermented by yeast.

Another method which gives more definite results is the aldol condensation of "glycerose" which is obtained by the oxidation of glycerol. When glycerol is oxidized the product formed is mostly dihydroxyacetone, $\text{CH}_2\text{OHCOCH}_2\text{OH}$, but some glyceraldehyde, $\text{CH}_2\text{OHCHOH}\cdot\text{CHO}$, is formed. The mixture is called glycerose. The formation of fructose by aldol condensation of dihydroxyacetone and glyceraldehyde is pictured below and is analogous to the condensation of acetaldehyde (p. 108).



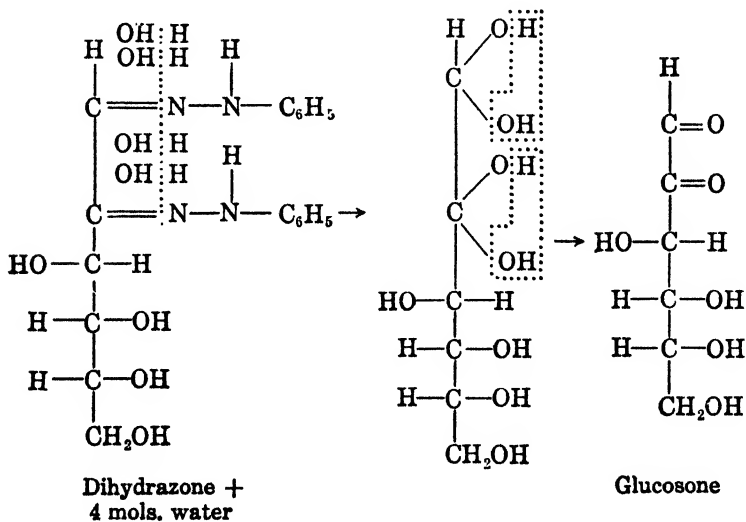
It is thought that some of the dihydroxyacetone comprising the "glycerose" is changed into glyceraldehyde by the dilute alkali which is used to promote the aldol condensation. This may take place in the following two steps, analogous to the reversible conversion of fructose to glucose.



When "glycerose" undergoes condensation there is a mixture of sugars formed, but out of this mixture Fischer was able to isolate a sugar which he first called *α-acrose* but which he later identified as *DL-fructose*. There has been no practical way devised for resolving a *DL*-mixture of sugars such as *DL-fructose* and for saving both forms of the sugar. If an organism is allowed to act on the mixture, the *L*-variety would probably be saved but the *D*-variety (the naturally occurring form) would be lost. Alkaloids cannot be employed because they do not react with the sugars. In the following paragraphs it will be shown how out of this *DL-fructose*, three naturally occurring sugars have been obtained, namely, *D-mannose*, *D-glucose*, *D-fructose*.

If *DL-fructose* is reduced, *DL-mannitol*, $\text{CH}_2\text{OHCHOHCHOHCHOHCHOHCH}_2\text{OH}$, is formed, and this can be oxidized to *DL-mannonic acid* with the formula $\text{CH}_2\text{OHCHOHCHOHCHOHCHOHCOOH}$. This *DL-mannonic acid* can be resolved into its optical isomers by the use of an alkaloid, and the *D*-form can then be reduced to the naturally occurring aldose sugar, *D-mannose*.

When *D-mannonic acid* is heated with quinoline, an interesting change takes place whereby part of it is converted into *D-gluconic acid*. This change amounts to a partial racemization (epimerization), as it consists of the inversion of the configuration involving the *one* carbon atom next to the carboxyl group. This one group (probably due to enolization) is more susceptible to racemization than the other asymmetric groups. The *D-gluconic acid*, which forms a lactone easily, can be reduced in this form to *D-glucose*.



Further, if either *D*-mannose or *D*-glucose is converted into a dihydrazone, the product is the same as the dihydrazone obtained from fructose. Upon treating this substance with fuming hydrochloric acid the phenylhydrazine residues are split off (by hydrolysis), forming a substance with both aldehyde and the ketone group, called *glucosone*. On reduction of the aldehyde group this glucosone yields *D*-fructose.

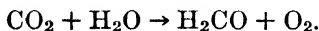
We have seen how it is possible to synthesize three naturally occurring simple sugars, using glycerol as the starting material. Previously (p. 238) we have mentioned the synthesis of glycerol. The simpler substances used can be synthesized from the elements. It is therefore possible to build up naturally occurring sugars from the elements which compose them. From the standpoint of structural chemistry this is an outstanding achievement.

Photosynthesis. In the presence of sunlight or other light containing the effective wave lengths, green plants are capable of synthesizing simple sugars from carbon dioxide and water. From these simple sugars more complex carbohydrates are derived, and other complex organic compounds are built up, such as proteins and fats. The process of photosynthesis is at the basis of all life. Animals depend ultimately on plant food, and the presence in plants of food which is capable of sustaining life is due to the process of photosynthesis.

Photosynthesis depends on the presence of the chlorophyll (p. 579) or the green coloring matter of the plant and on the radiant energy. Chlorophyll is not a single substance, however, and acts only in conjunction with other substances in a manner that is little understood, and cannot be discussed here. Energy must be absorbed in the conversion of carbon dioxide into sugars, for the change is endothermic. This energy is supplied by the sunlight and is stored up in the products of photosynthesis. When the carbohydrates are used as food and are burned in the body metabolism, the energy is liberated.

It has long been suspected that the first product formed in the photosynthetic process is formaldehyde, and that by some special mechanism this is polymerized into certain definite sugars. We have already noted that formaldehyde polymerizes readily, in the presence of very weak alkali, into *formose* which is a mixture of probably a large number of sugars. The formation of for-

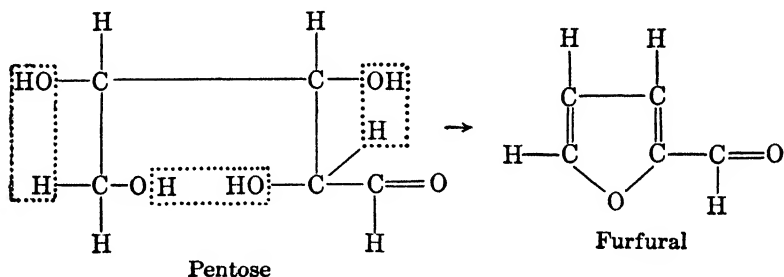
maldehyde from carbon dioxide and water may be pictured by the equation



Oxygen is of course known to be given off by plants during photosynthetic activity.

The process of photosynthesis may be much better understood in the near future through the use of heavy carbon, C_{18} , and radioactive carbon, C_{14} , as tracer elements (p. 626).

Action of Acids on Simple Sugars. When pentose sugars or more complex carbohydrates which produce them on hydrolysis are heated with hydrochloric acid, they are almost quantitatively converted into *furfuraldehyde*, more commonly called *furfural*. This reaction with concentrated acid is a dehydration and takes the course pictured below.



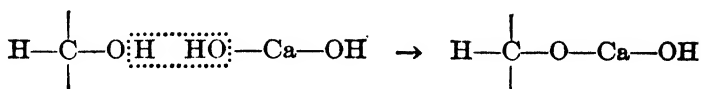
The product is an inner ether, is doubly unsaturated, and retains the aldehyde characteristics of the pentose. The five membered ring of which oxygen is one member is relatively stable, as will be discussed later. Furfural is prepared commercially from oat hulls, which contain *pentosans* or substances which hydrolyze to give pentoses (p. 339).

If hexoses are heated with strong acids, complicated reactions take place which follow no single well-defined course. If glucose is allowed to stand in contact with cold hydrochloric acid, condensation to more complex sugars takes place. This reaction will be discussed later.

Action of Bases. Heating glucose or fructose with a sodium hydroxide solution causes profound changes in the structure of

the molecules, and a considerable part of the simple sugar may be converted in this way to lactic acid, which has a molecular formula just half that of the sugar. The splitting apart of carbon atoms by the action of alkali has been encountered many times before. When a solution of a simple sugar is made even slightly alkaline in reaction, important changes take place. We have already noted the reversible conversion of glucose, mannose, and fructose into each other under these conditions. In addition to this the simple sugars in alkaline solution become very easily oxidized, in fact, they absorb oxygen readily from the air when it is bubbled through the solution. Even very slight alkalinity is sufficient to make the sugar much more susceptible to oxidation.

Glucose and the other simple sugars, like other substances which have more than one hydroxyl group in their structure (p. 239), are able to dissolve metallic oxides and hydroxides by combining with them to form salt-like compounds. They thus show acidic properties stronger than the simple alcohols. Glycol for example bears the same relation to ethyl alcohol that hydroxyacetic acid bears to acetic acid. The same effect that causes hydroxyacetic acid to be much stronger than acetic acid causes the glycol to have stronger acid properties than the simple alcohol. This effect is even greater in the sugars. With lime and baryta, glucose forms calcium and barium glucosates which are of the nature of basic salts. One of the alcohol groups is involved, in the following manner:



The glucosates and similar derivatives of the other simple sugars are soluble in water.

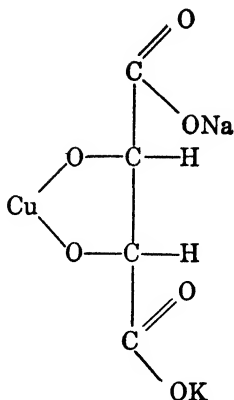
Oxidation. In the study and quantitative determination of simple sugars, use is made of the ease with which they are oxidized. By the careful use of bromine water the aldoses can be oxidized to monocarboxylic acids (gluconic, galactonic, arabinonic, etc.) or by more drastic treatment to dicarboxylic acids as previously indicated. Both aldoses and ketones reduce am-

moniacal silver solutions very readily, and it is interesting to note that the ketoses are generally more quickly oxidized than the aldoses under similar conditions. This is probably due to the tautomeric forms in which the different sugars exist. The formulas which we use to designate the various sugars, as we well appreciate, are imperfect, and do not picture all of the tautomers and the rate at which they pass from one form to another. It is possible that glucose is converted to its easily oxidized form less quickly than is fructose. Both glucose and fructose are, in the end, able to take up almost exactly the same amount of oxidizing agent under the same conditions. It may be said that hydroxy ketones generally are like the aldehydes in their ease of oxidation.

Fehling's³ solution is a valuable reagent for the study of easily oxidized organic substances. It consists of a solution of sodium potassium tartrate, sodium hydroxide, and copper sulfate. The solution is usually kept in two parts, "A" and "B," which are mixed in equal proportions when the solution is to be used. If mixed previous to use and kept for some time, the tartrate is oxidized by the copper sulfate. The "A" solution contains 69.278 grams of crystallized copper sulfate per liter, while the "B" solution contains 346 grams of sodium potassium tartrate and 100 grams of sodium hydroxide per liter. For quantitative work the concentration of the various ingredients, especially the copper sulfate, which is the oxidizing agent, must be definite.

The copper sulfate furnishes cupric ions which, under the conditions used, are reduced to the cuprous form which precipitates as red cuprous oxide. The sodium hydroxide is present to make the solution alkaline so that the substance under investigation will be easily oxidized. If a copper sulfate solution is made alkaline with sodium hydroxide, the copper is precipitated as hydroxide, so no oxidizing agent is left in the solution. To avoid the precipitation of the cupric hydroxide, sodium potassium tartrate is used. This reacts with cupric hydroxide to form a salt-like compound of the following structure.

³ H. Fehling (1812-1885) was Professor of Chemistry at Stuttgart.



This substance remains in solution, furnishes a low concentration of copper ions, and at the same time the solution is alkaline.

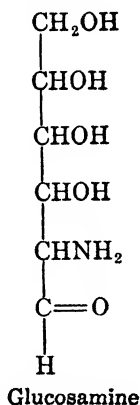
Fehling's solution does not have strong oxidizing action, and so will not oxidize substances unless they are very easily oxidized. Alcohols, acids, ordinary ketones are not affected, but aldehydes, hydroxy ketones and some other very easily oxidized substances to be studied later (di- and tri-phenols, etc.) are oxidized readily by the action of Fehling's solution.

There are a number of possible solutions which may be used in the same manner as Fehling's solution. For example, salts other than copper salts may be used, such as those of bismuth and mercury. There is no special virtue in the sulfate of copper, other than its cheapness, so that other copper salts may also be used. Instead of sodium potassium tartrate any polyhydric alcohol may be used, since they all act with cupric hydroxide in the same manner. Glycerol or even cane sugar (which does not reduce Fehling's solution) may be used for this purpose. To get uniform results, however, the materials must always be the same. Fehling's solution is very convenient, and is often used as an oxidizing solution for the study of sugars and other highly reducing compounds.

When a solution containing a certain amount of glucose, for example, is heated with Fehling's solution, a precipitate of cuprous oxide is soon formed and the oxidation is complete after a few minutes. By determination of the amount of cuprous oxide formed either gravimetrically

or in some other way, which may be direct or indirect, the amount of glucose which was in the original sample may be determined. This scheme, which has been used with many modifications, serves as a convenient method for the quantitative determination of reducing sugars when other very easily oxidized substances are known to be absent. Fehling's solution is of such strength that 50 milligrams of glucose is required to reduce completely 10 ml. of the solution, under a given set of conditions. Fehling's solution contains about 88 milligrams of copper in 10 ml. (1.38 mg. mol.) and this amount is sufficient to oxidize 50 milligrams of glucose (.277 mg. mol.). This is in the proportion of five atoms of copper to each molecule of the glucose. No single definite product is formed from the glucose by oxidation with Fehling's solution, but under uniform conditions, the oxidation takes place to the same extent.

Glucosamine, an Amino Sugar. When *chitin*, the bony shell material of crustacea, is hydrolyzed, one of the substances which is formed is *glucosamine*, for which the following structure has been proposed.



This is the same as the formula for the aldo-hexoses except that one hydroxyl is replaced by an amino group. This substance is of some importance as it is a hydrolysis product of some of the glycoproteins. Glucosamine in combination with acetic acid, sulfuric acid and *glycuronic acid*, $\text{CHO}(\text{CHOH})_4\text{COOH}$, makes up a complex acid known as *chondroitic acid*, which is the non-amino-acid part of conjugated proteins from cartilage.

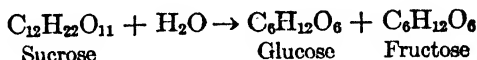
Disaccharides

There are three important sugars occurring in nature which have the molecular formula $\text{C}_{12}\text{H}_{22}\text{O}_{11}$, namely, *sucrose* (ordi-

nary cane sugar) *lactose* (milk sugar) and *maltose* (malt sugar). These break down on hydrolysis into simple sugars.

Sucrose is the most important of these, from the standpoint of its occurrence and use. It is extracted commercially from sugar cane, and sugar beets, but is present in smaller quantities in a very large number of plant juices. Cane and beet sugar as they come from modern refineries are practically identical. The preference of some housewives for cane sugar probably has its basis in the fact that when beet sugar is not highly refined it contains impurities which are bitter tasting and objectionable. If, on the other hand, a small amount of the molasses is left in cane sugar, the resulting product has a slight flavor like that of brown sugar, which contains a considerable amount of molasses. Maple sugar is principally sucrose but contains in addition the characteristic flavoring which makes it especially valuable.

Cane sugar, *sucrose*, or *saccharose* breaks up upon hydrolysis into equal amounts of glucose and fructose according to the following equation:



Cane sugar is *dextrorotatory* with a specific rotation of $+66.5^\circ$ at 20° . The products of hydrolysis are: *dextrorotatory* glucose with a specific rotation of $+52.6^\circ$ after equilibrium is attained, and *levorotatory* fructose with a specific rotation of -93° . Since the fructose is more strongly *levorotatory* than glucose is *dextro*-rotatory, the mixture after hydrolysis is *levorotatory*. On hydrolysis the rotation changes from *dextro* to *levo*, and it is for this reason that the process of hydrolyzing sucrose is often spoken of as *inversion*, and the mixture of glucose and levulose formed by the hydrolysis is called *invert sugar*.

Determination of Sucrose by Means of a Polarimeter. The principle involved in the determination of cane sugar by the use of any instrument which measures optical rotation is illustrated by the following examples. The specific rotatory power of cane sugar is 66.5° , which means that if we could have a solution containing 100 grams of sugar per 100 ml. of solution, one decimeter of this solution would cause a rotation of 66.5° . One decimeter of a solution containing 20 grams per 100 ml.

causes a rotation $1/5$ of this value or 13.3° and other solutions cause rotation in proportion to their strength.

Frequently the case is more complex than this since other optically active substances may also be present. Invert sugar is the impurity most often present. In this case, use is made of the fact that most substances are not affected in their rotatory power by a mild treatment with acid whereas sucrose is changed to invert sugar and is thus greatly affected. Suppose that a decimeter of a solution containing 20 grams of sucrose per 100 ml. is tested and found to rotate the plane of polarized light 13.3° . Suppose that this solution is then treated in a definite way with acid to hydrolyze the sucrose and an equivalent amount is again tested in the polarimeter. Each gram of sucrose produces on hydrolysis approximately 1.059 grams of invert sugar, the increase being due of course to the water taken up on hydrolysis. The invert sugar solution formed would contain 21.18 grams per 100 ml. and will give a rotation of -8.26° . (Specific rotation of invert sugar is -39° at 20° .) The algebraic difference between the positive rotation of the original sugar and the negative rotation of the invert sugar is therefore 21.56° .

This *difference* of rotation would be the same for all solutions containing originally 20 grams of sucrose per 100 ml. no matter what other optically active substances are present, provided the other substances are unaffected in rotatory power by the acid treatment. Let x be the rotation due to the other optically active substances, then the original reading on the solution would be $(13.3 + x)$ degrees. The reading after inversion would be $(-8.26 + x)$ degrees. In obtaining the algebraic difference x is eliminated.⁴

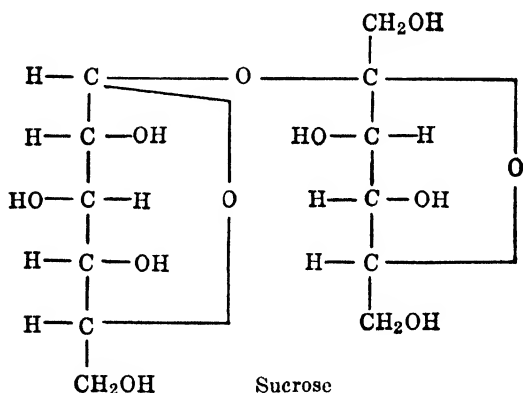
As many as sixteen different scales for measuring optical rotation have been in use and many of these have been used for sugar determinations. The *Ventzke* scale and instrument are now most in use. This instrument is graduated in such a way that when 26 grams of the crude sugar to be analyzed is made up to 100 ml. solution, the percentage of sugar in the sample is read off directly on the scale. This gives the actual percentage only when no other optically active substances are present. By comparison of the percentage obtained in this way with the percentage which is indicated by specific gravity of the syrup, the percentages of both sucrose and invert sugar can be obtained from

⁴ Suppose a syrup is being tested quantitatively for sucrose, which contains invert sugar and possibly other optically active substances. Twenty grams of this syrup is made up to 100 ml. of solution, and the reading for a one-decimeter tube is 7.7° . After inversion the reading is -5° . The difference between the positive and negative reading is 12.7° . If the syrup had been pure sucrose, the difference would have been 21.56° . The amount of sucrose in the syrup is therefore $12.7/21.18$ or about 59 per cent.

specially prepared tables. Extensive use is made of determinations of this sort in sugar refineries.

Chemical Properties and Structure of Sucrose. The outstanding characteristic of sucrose as contrasted with the other disaccharides and with monosaccharides is that it is not a "reducing sugar," that is, it is not easily oxidized like lactose, maltose and all the simple sugars. From this it is inferred that sucrose is neither an aldehyde nor a hydroxy ketone. It does not have the properties shown by substances which have the characteristic sugar group ($-\text{CHOHCO}-$) in their structures.

The most probable structure of sucrose is indicated below :



It is clear from the formula that sucrose is both a glucoside and a fructoside, that is, both the potential aldehyde and ketone groups are involved in the linkage of the two residues. This explains its lack of reducing properties because neither glucosides nor fructosides have reducing properties unless they possess a reducing group elsewhere in the molecule. It also is in accord with the fact that sucrose is readily hydrolyzed compared with other complex sugars. The carbon atoms in both residues, which are linked by oxygen, have a second valence attached to oxygen, hence sucrose is the anhydride of stronger "acids" than would otherwise be the case (p. 158).

It should be noted also that in glucose residue there is the normal pyranose (six membered) ring while in the fructose resi-

due the ring is five membered (furanose). There is abundant evidence to indicate that when sucrose undergoes hydrolysis, there is *in addition to the hydrolysis* a change in the fructose whereby it becomes *levorotatory* instead of *dextrorotatory* as it is in the sucrose molecule. It is supposed that this change in direction of rotation accompanies a change from the five membered ring in the sucrose molecule to the six membered ring of the fructose in its normal condition.

That inversion of sucrose involves something other than simple hydrolysis is evidenced by the fact that octamethyl sucrose (in which ring changes would not be possible after hydrolysis) does not "invert" on hydrolysis. Its rotatory changes only from +66.5 to +56.5. Sucrose can also be hydrolyzed by active enzyme preparations under such conditions that there is evidence of *hydrolysis* previous to *inversion*. The latter takes place as a secondary reaction.

General Properties. When heated, sugar melts at 160° and upon further heating becomes yellow and finally brown in color. At about 200° *caramel* is formed by loss of water. It is probably not a definite compound but it can be made uniform in quality and is used as a coloring and flavoring matter. When heated to a still higher temperature the complex sugar molecules "go to pieces" and a number of substances of various kinds are produced. Carbon monoxide, carbon dioxide, methane, ethylene, acetylene, formic acid, acetic acid, acetaldehyde, acetone, and acrolein are substances which are said to be formed during this decomposition.

If sucrose is treated with concentrated sulfuric acid, it turns very black due to the carbon which separates as a result of dehydration. This behavior is in accord with the suggested structure because hydrogen atoms and hydroxyl groups which are on adjoining carbon atoms are generally easily removed, and most of the hydrogen and oxygen could be removed in this way from a substance with the structure suggested.

In the extraction of sucrose from beet molasses use has been made of the fact that sucrose reacts with basic oxides to form salt-like compounds, which are similar to the compounds which are formed by the monosaccharides. Sugar will not readily crystal-

lize from beet molasses though its sugar content is high. In addition to sucrose the residual molasses contains invert sugar, also gums, nitrogenous compounds and salts. When the price of sugar justifies it, extreme measures are taken to extract all the sugar out of the molasses that it is possible to recover. In one method the material is treated with lime, and insoluble tricalcium sucrate (saccharate) is formed. In some cases the corresponding tristrontium sucrate is precipitated. These precipitates after separation by filtration are decomposed with carbon dioxide which produces insoluble carbonates, and leaves the sugar in solution free from many of the impurities and thus freer to crystallize. When a solution of sucrose is treated with calcium hydroxide at low temperature, only the soluble monocalcium and dicalcium sucates are formed. When the solution is boiled the tricalcium salt is formed and being insoluble precipitates. This behavior is probably analogous to the action of glycol on metallic sodium, in which case only one hydrogen atom is replaced at ordinary temperatures but at higher temperature the second hydrogen is replaced. The structures of the sucates are probably similar to the corresponding derivatives of the simple sugars already mentioned.

The Manufacture of Sugar. The world's yearly production of sugar amounts to about 35,000,000 tons of which about two-thirds is cane sugar and one-third beet sugar.

The production of raw sugar from either sugar cane or sugar beets involves the following operations: (1) extraction, (2) clarification of the juice, (3) concentration of the juice, (4) crystallization from the syrup, (5) separation of the crystals, (6) working over of mother liquors. In the case of cane sugar manufacture the extraction is by macerating the sugar cane and pressing out the juice by running the pulp through a series of rollers. Some water is sprayed on the pulp as it passes from one set of rollers to the next. By this means it is possible to extract 95 per cent of the sugar from the cane. The juice is clarified by treating it with milk of lime, which neutralizes the acidity and causes the formation of a flocculent precipitate which carries down many of the impurities and leaves a clear juice. The clarified juice is then evaporated in a multiple effect evaporator under diminished pressure until it contains about 55 per cent solids. It is then transferred to a "vacuum pan" where the concentration is continued until the material is a mass of crystals and mother liquor containing only 6 or 8 per cent water,

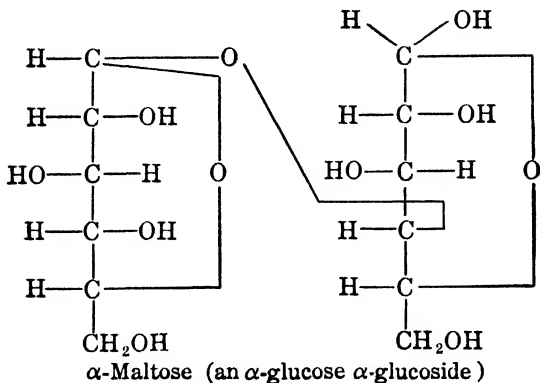
called the "massecuite." This mass is whirled rapidly in perforated drums (centrifuges) and most of the mother liquor is thereby removed. The raw sugar then remaining in the drums may be sprayed with a small amount of water and centrifuged to remove further molasses. The raw sugar is now ready for the refinery, while the molasses may be worked over and further sugar obtained from it. This may be accomplished by evaporating to the proper consistency and then running it into crystallizers where it is stirred continuously, for a considerable time. The molasses is separated from the crystalline sugar by centrifuging as before.

In the manufacture of beet sugar the extraction is carried out by the diffusion process. The beets are sliced into long fine shreds, which are extracted with water, by a continuous process. The extract passes from one unit to another in succession, and becomes more and more concentrated as it passes. As it leaves the final unit, it contains 12 to 15 per cent sugar. To clarify the juice it is treated with an excess of lime, which is then precipitated by introducing carbon dioxide gas. This precipitate carries down a large amount of suspended matter and clarifies the juice. The filtered extract is then further purified by treatment with sulfur dioxide, or by a second treatment with lime at a higher temperature. By this means the juice may be obtained practically colorless, and from it, by evapoartion, sugar can be obtained which is ready for marketing.

The refining of sugar, especially in the case of cane sugar, is an operation which is separate from the manufacture of crude sugar. Cuban and Hawaiian raw sugar, for example, are brought for refining to the United States. The refining of sugar involves the following steps which will not be discussed in detail: (1) preliminary washing of the crude sugar with syrup and a small amount of water followed by centrifuging, (2) dissolving crude sugar in a small amount of water, (3) clarification of solution by treatment with lime and phosphoric acid and filtering, (4) decolorizing the amber-colored liquor by filtration through bone charcoal, (5) evaporation and crystallization of the colorless syrup, (6) separation and drying of crystals, (7) reworking of mother liquors.

Maltose. The hydrolysis of maltose is more difficult than that of sucrose but it may be represented by the same molecular equation. From each molecule of maltose two molecules of *D*-glucose are obtained, and in the maltose structure itself one of the aldehyde groups must be potentially free, since maltose reduces Fehling's solution and an ammoniacal silver solution. Other evidence for the presence of an aldehyde group in maltose is its

reaction with phenylhydrazine. Following is a representation of the maltose structure.



It exists in two epimeric (and tautomeric) forms of which only one (the α form) is represented above. In accordance with this, maltose shows mutarotation. It is pictured as an α -glucoside in which the configuration of the fifth asymmetric carbon atom in the residue on the left is the same as that in α -methyl glucoside. The evidence for this is based partly on its behavior with enzymes and partly upon a study of rotatory powers.

Maltose occurs in malted barley, as well as in many other sprouting grains. It is formed in these cases by hydrolysis from starch, which is a more complex carbohydrate. It is probable that in the hydrolysis of starch maltose is always formed as an intermediate product. Maltose crystallizes in needles, and is strongly *dextrorotatory* in solution ($[\alpha]_D^{20} = +136.9^\circ$).

Lactose. The hydrolysis of lactose can be accomplished in exactly the same way as that of maltose, by heating with acids, and the same molecular equation may be used to picture the reaction. The monosaccharides formed in this case are *D*-glucose and *D*-galactose. About 4 per cent of the total weight of milk is lactose and this constitutes the only important source. It is prepared technically to some extent from milk after the fat and casein have been removed for butter and cheese making. By evaporation of the liquor to a definite point, after most of the proteins have been separated, impure lactose crystallizes out on cooling and may be refined by the usual methods.

Lactose is like maltose in that it reduces Fehling's solution and ammoniacal silver solutions. In alkaline solution both lactose and maltose are easily oxidized like the simple sugars and their alkaline solutions turn brown on heating.

The structure of lactose is identical to that of maltose (p. 364) insofar as the right hand portion is concerned. It differs in that it is a β -galactoside. The residue on the left has the galactose configuration. That this sugar is a galactoside instead of a glucoside is shown by the fact that careful oxidation followed by hydrolysis yields galactose and gluconic acid rather than glucose and galactonic acid as would be the case if it were a galactose glucoside.

Synthesis of Disaccharides. The direct condensation of simple sugars to form disaccharides has been accomplished, though the resulting disaccharides have not always been the ones which it was desired to prepare. For example, when glucose was allowed to stand in the cold in the presence of hydrochloric acid, a disaccharose formed which was not maltose but an isomer which has been called *isomaltose*. There are obviously different ways in which two molecules of glucose can condense and in this case the product was not the naturally occurring disaccharose. Subsequently it has been found that some maltose is formed simultaneously with isomaltose.

Maltose has also been synthesized in other ways, and various other disaccharides have been synthesized but not the more common ones. The synthesis of sucrose has been reported on two different occasions but both times has failed of confirmation.

Fermentation and Enzyme Action

The properties of the sugars can hardly be studied without a consideration of fermentation and related processes and the means by which they are accomplished. The alcoholic fermentation of solutions containing sugars has been known since antiquity and was utilized in the making of fermented liquors long before the existence of the substances involved in the process was recognized. Early in the study of fermentation it was definitely shown by Pasteur that the alcoholic fermentation is caused by

living yeast cells, and that other kinds of fermentation are caused by other organisms. Near the end of the nineteenth century, Buchner⁵ succeeded in showing, however, that the juice of yeast cells, prepared by breaking the cells and submitting them to high pressure, will cause fermentation when there are no live yeast cells present. It had previously been shown that certain plant extracts were capable of causing definite chemical changes to take place so that this discovery of Buchner was not entirely unique. However, the action of yeast has claimed much attention from those who have studied changes of this type. The term *enzyme* (from the Greek, meaning "in yeast") is used to designate those substances which are present in organisms and can bring about various chemical reactions.

The resemblance between the action of the so-called enzymes and that of inorganic contact catalysts was early noted and the best evidence goes to show that enzyme action is a type of catalytic action which is commonly associated with living organisms. Though it is possible to isolate from yeast a non-living mixture which will cause fermentation, it is not possible as yet to obtain material that will accomplish this result from other than living sources.

From a consideration of the structure of glucose and the equation of alcoholic fermentation, $C_6H_{12}O_6 \rightarrow 2CO_2 + 2C_2H_5OH$, it is obvious that the transformation involved must be a highly complicated one. This is indeed true and extensive studies have revealed that a considerable number of specific enzymes (colloidal and heat labile) and coenzymes (non-colloidal and heat stable) are necessary for the complete transformation. Phosphates are essential to the process and esters of phosphoric acid are among the intermediate products. Originally "the" enzyme catalyzing the process was called "*zymase*."

In recent years several enzymes have been obtained in pure form. They are protein in nature and hence colloidal. If the colloidal condition is destroyed, the activity of the preparation is destroyed at the same time. The colloidal condition of enzyme

⁵ E. Buchner (1860-1917) was Professor of Chemistry at Breslau and later at Wurzburg.

preparations and their activity is generally destroyed at temperatures considerably below the boiling point of water.

Enzyme reactions like others are affected by temperature. Frequently the optimum temperature for enzyme actions is near body temperature (37°) but enzymes differ in this respect. Enzymes are also greatly affected by hydrogen ion concentration. Most enzymes are most effective at fairly definite acidities; the enzymes of the stomach act in acid solution while those in the intestine are active in nearly neutral condition.

The numerous names for the different enzymes are often names for more or less hypothetical substances, which are recognizable only because of the effects which they may produce. Generally a definite enzyme preparation can accomplish only a definite result; for example, a crude preparation of "*zymase*" can be obtained which will cause alcoholic fermentation, but will not cause the hydrolysis of cane sugar into glucose and fructose. Another preparation in the form of a powder can be obtained from yeast in another way, which in solution is capable of causing a rapid hydrolysis of sucrose at room temperature. This preparation is, however, incapable of converting glucose or fructose into carbon dioxide and alcohol. The second preparation is said to contain *invertase*, an enzyme capable of "inverting" cane sugar.

Some enzyme preparations, however, are capable of causing a good many changes of similar character to take place. This is true of many of the so-called *proteolytic* or protein hydrolyzing enzymes. Pepsin, which may be extracted from hog's stomach lining, is capable of breaking down almost any naturally occurring protein into simpler substances of a complex polypeptide nature, without, however, converting them into amino acids. In the digestion of foods in the body the further conversion to amino acids takes place in the small intestine where several different enzymes are present.

It is probable that a great many of the chemical reactions which are known to take place constantly in all organisms are brought about by agencies which might be termed enzymatic, because a great many of these reactions cannot be made to take place in the laboratory under similar conditions. It is impossible

to understand much about the wide scope of enzyme action without delving deeply into physiological chemistry, or biochemistry.

The following list of enzymes will serve to give some idea of the reactions which are promoted by enzyme catalysts; the list is not intended to be inclusive.

Amylases, which bring about the hydrolysis of starch; found in digestive juices, in all germinating seeds, especially barley (*diastase*); are capable of being developed wherever starch occurs in nature.

Lipases (s. lī'pās), which bring about the hydrolysis of fats; found in the stomach and intestine, as well as in fatty seeds, etc.

Proteases, which bring about the hydrolysis of proteins; found in the digestive juices, *pepsin* in the stomach, *trypsin* in the intestine; in plants, especially in germinating seeds; also in microorganisms.

Invertase, *maltase*, and *lactase* bring about the hydrolysis respectively of sucrose, maltose, and lactose, and occur in different yeasts and other microorganisms as well as in the digestive tract. Maltase is of particular importance because it catalyzes the hydrolysis of α -glucosides generally.

Glycogenase, which, in the liver, brings about the hydrolysis of glycogen.

Urease, extracted for example from the soy bean, promotes the hydrolysis of urea.

Carboxylases, from microorganisms, etc., bring about the removal of the carboxyl group from amino acids.

Deaminases remove the amino group from amino acids, etc.

Emulsin is one of a large number of enzymes which bring about the hydrolysis of β -glucosides.

Oxidases, which are very widely distributed in nature. The darkening of the flesh of fruits such as bananas or apples on exposure to air is caused by oxidation brought about by enzymatic action. This oxidation is now being controlled by the use of an antioxidant, ascorbic acid (Vitamin C, p. 601).

Dehydrogenases catalyze the dehydrogenation (oxidation) of various specific compounds.

So-called *catalase* brings about the decomposition of hydrogen peroxide. This enzyme occurs in actively growing tissues, in the blood, saliva, etc., hence the bubbling when peroxide is placed in the mouth or in contact with broken skin.

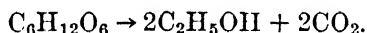
Autolysis is a process which takes place by enzyme action. When yeast, for example, is allowed to stand at a moderate room temperature in the absence of foreign organisms, and without suitable food to grow upon, it dies and undergoes auto-digestion. The proteins of the original yeast are broken down into simpler substances, and other complex compounds undergo like change under the influence of the enzymes which are present in the yeast. The same kinds of changes take place in all organisms after death. Generally foreign organisms are present and these introduce enzymes which are capable of causing putrefaction. However, if these organisms are completely excluded, changes take place nevertheless. In the preservation of foods enzymes both from foreign organisms and originating in the food itself must be destroyed or held in check. When food is sterilized by heat, foreign organisms are killed and the natural enzymes are destroyed. When the food is dried, the enzymes are rendered inactive by unfavorable conditions (lack of water); when preserved by "quick freezing" the enzymes are largely inactive due to low temperature. With vegetables it is necessary to use a short period of heat (blanching) before freezing to inactivate to a large degree the enzymes which are present. Enzymes from microorganisms or present in the food are responsible for changes occurring during the ripening of cheese or the ageing of meat.

Fermentation of Sugars. All of the seven naturally occurring sugars (glucose, mannose, galactose, levulose, sucrose, lactose, maltose) which have been discussed, except lactose, are fermentable by ordinary yeast, and lactose is fermented by a certain type of yeast (*torulae*). The inability of ordinary yeast to ferment lactose is due to its lack of an enzyme (lactase) capable of breaking lactose into glucose and galactose because both of

these simple sugars are fermented by yeast. Both maltase and invertase on the other hand are present in yeast.

If, instead of naturally occurring *D*-glucose, one attempts to ferment artificially prepared *L*-glucose, failure results, as the optical antipode is unaffected. This is in accord with the fact previously noted that optical antipodes are biologically different substances. The situation has been compared to the relation which exists between lock and key. The substance to be acted on is compared to the lock and the enzyme which is capable of acting only on this particular substance, to the key. Sometimes there is a markedly specific ability of an enzyme to attack one single substance and no other. However, there are other cases in which the enzyme may aptly be compared to a master key which is capable of unlocking many different locks. Because of the fact that certain organisms are able to attack only certain sugars, use is frequently made of rarer sugars to study micro-organisms. Two organisms may be difficult to differentiate except by testing their ability to ferment a certain sugar.

The reaction of alcoholic fermentation is approximately represented by the equation.



As fermentation is actually carried out there are a large number of substances formed along with the alcohol and carbon dioxide; among these are a mixture of amyl alcohols (fusel oil),⁶ small amounts of all of the lower alcohols, succinic acid,⁶ glycerol, acet-aldehyde and other aldehydes, acetic and formic acids, and several esters. All of these substances are formed simultaneously. When the yeast juice prepared according to Buchner is used to carry on the fermentation most of these secondary products disappear, as they are associated with phases of yeast metabolism other than the fermentation itself.

⁶ These compounds do not come from carbohydrates but from the following amino acids which are usually present in the fermenting mixture: leucine (isoamyl alcohol), isoleucine (*d*-amyl alcohol) and glutamic acid (succinic acid).

Polysaccharides

The term "polysaccharide" is often applied to those carbohydrates which are more complex than the disaccharides. The most important members of this class have very high molecular weights but there is one trisaccharide and a tetrasaccharide which should be mentioned. *Raffinose* ($C_{18}H_{32}O_{16}$) is found along with ordinary sugar in beet juice. Unfavorable conditions of growth increase its formation. On hydrolysis it yields equal quantities of *D*-glucose, *D*-galactose, and *D*-fructose. *Stachyose*, ($C_{24}H_{42}O_{21}$), is a naturally occurring tetrasaccharide, each molecule of which on hydrolysis produces one molecule of *D*-glucose, one molecule of *D*-fructose, and two molecules of *D*-galactose.

Starch is a familiar term applied to a complex carbohydrate (or group of carbohydrates) which is found abundantly in plants, and which corresponds in composition to the empirical formula $C_6H_{10}O_5$ but has a high molecular weight.

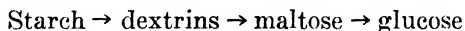
It is of tremendous importance in nature. It is the most important reserve fuel for organisms in general. Plants store large quantities in seeds and tubers which may be broken down and utilized by the plants or consumed by animals. It is the most important fuel-food used by mankind. For this purpose it is usually not separated from the accompanying materials, but for some purposes starch must be purified.

The complexity of starch is shown by the fact that unlike sugars, starch does not dissolve in water and therefore is tasteless. Starches from different plants appear under the lower powers of the microscope as granules of different sizes and shapes which are somewhat characteristic for a given source. In corn starch the outer layer is of slightly different composition and more resistant to hydrolysis and contains a small amount of phosphoric acid in combination. This outer layer is known as *amylopectin*. The inside portion of the granules which is practically free from phosphoric acid is known as *amylose*. (Potato starch does not show much contrast between the inner and outer layers. Both portions contain phosphoric acid in combination.)

When the granules of corn starch are broken by heating, mild

acid treatment or mechanical grinding the amylose goes into colloidal solution. "Soluble starch" which is a colloidal material is made by treating starch with cold dilute acid.

When starch is treated with dilute acid or heated to about 200° dry ⁷ it yields *dextrins* which are partial hydrolysis products and are used as adhesives, for example on postage stamps. Further acid treatment causes hydrolysis which may be summarized as follows,



Starches from different sources give with free iodine a blue or blue-black coloration which disappears on heating or upon the addition of alcohol. It is thought that the iodine and starch form a loose chemical compound which is intensely colored, and that this compound dissociates to some extent into free iodine and starch. Upon heating this dissociation takes place practically completely, and the blue color disappears. Alcohol by readily dissolving the iodine is also thought to shift the equilibrium so that none of the blue compound remains.

In America, corn is used as a source for the manufacture of starch; many million bushels are used yearly for this purpose. There is little chemistry involved in the separation of the starch from the grain. The grain is softened by the use of a sulfurous acid solution. For separating the germ from the rest of the grain after grinding, use is made of the fact that the germ contains much oil and therefore floats on water while the rest of the grain sinks. By means of a great many grindings, washings, screenings and settlings, the starch is separated from the germs, protein material and bran, in quite pure form.

Much of the starch that is produced is converted by hydrolysis with dilute sulfuric acid into glucose, which is practically the only hydrolysis product. Starch is also used in the preparation of foods; in modified form as laundry starch, and for sizing and loading paper goods, etc., and is converted by mild acid treatment into dextrins which are used as adhesives.

⁷ Starch which appears dry contains a certain amount of tightly bound water which may enter into the hydrolysis in this case.

Inulin is a substance very much like starch in general appearance and properties, except that it dissolves in water more readily and gives a yellow instead of blue color with iodine. It is not found so extensively in nature, but in Jerusalem artichokes, dahlia tubers and many other less common plants it plays the same rôle as that played by starch in the majority of plants. It hydrolyses to form levulose (*D*-fructose) exclusively, and is the principal source from which levulose can be prepared for laboratory or other use. Its empirical formula⁸ is the same as that of starch and it is of about the same complexity.

Glycogen is a colloidal polysaccharide which is found in the liver and in muscles. The total amount found in the muscles is approximately the same as that which is found in the liver. It is the form in which excess energy is stored temporarily in the body. The glucose from food which is finally to be utilized is changed into glycogen for storage. When needed, this glycogen is converted by enzymatic action into glucose which acts more or less directly as a fuel. Following the digestion of much carbohydrate food, the glycogen content of the body increases and upon exertion the glycogen content is diminished.

The method used for the isolation of glycogen illustrates the extreme stability of some of the colloidal polysaccharides to alkali. The liver of an animal which has, previous to its slaughter, been fed carbohydrate food, is digested in boiling 30 per cent potassium hydroxide solution. All of the protein material is converted to simple substances by this treatment and the glucose which is likely to be present is oxidized or otherwise decomposed. After filtration the glycogen is precipitated by adding alcohol, in which it is insoluble.

Glycogen forms an opalescent solution which rotates polarized light, $[\alpha]_D = +196.6^\circ$.⁸ With iodine glycogen gives a characteristic reddish color. It is sometimes called "animal starch," but since it occurs in some plants, *e.g.*, yeast, the name is hardly appropriate.

⁸ The optical rotation caused by solutions which are not perfectly clear is variable and untrustworthy; it depends somewhat on the way the solution is prepared.

Celluloses are the principal constituents of the cell walls of plants, and thus are the framework of the tissues. Cellulose is most familiar in the form of pure cotton, or in filter paper. All paper contains cellulose but paper which is used for writing or printing is sized and loaded so that in many cases it contains much besides cellulose.

Woods are composed mainly of cellulose in combination with *lignins*. Such combinations are known as "lignocellulose." Lignins are substances of rather indefinite chemical nature. In the manufacture of paper from wood it is necessary to remove the lignin, and this is often accomplished by treatment of the wood fibers with a solution containing sulfur dioxide and lime. It is thought that the active substance in this solution is calcium bisulfite, and that it reacts with the lignin (an aldehydic substance) to form soluble derivatives. At any rate, by this means, suitable woods are freed from lignin and converted into pulp, which is impure cellulose and is used in the manufacture of paper. For cheaper papers it is mixed with certain percentages of finely ground wood.

Celluloses from different sources are not exactly the same and "cellulose" cannot be regarded as a name for a perfectly definite chemical substance. The same is true of the other polysaccharides. Common forms of cellulose such as make up cotton and filter paper have the same empirical formula, $C_6H_{10}O_5$, as the other polysaccharides. Cellulose is relatively resistant to hydrolysis as compared with the other polysaccharides but upon boiling with dilute acid it eventually yields glucose with *cellobiose* (a glucose- β -glucoside) as an intermediate hydrolysis product.

A strong solution of alkali produces in cotton a gelatinizing of the fiber walls, which makes the fibers translucent and gives them a silky appearance. The change involves the reaction between the alkali and the acidic alcohol groups of the cellulose. This action was discovered by an Englishman named Mercer and the process of *mercerizing* cotton bears his name. Treatment of cellulose in the form of filter paper with a strong solution of sulfuric acid (one volume of water to two volumes of acid) produces a somewhat similar result. The paper becomes tough and

transparent through gelatinization, and is known as *parchment paper*.

Cellulose Esters and Ethers. Cellulose evidently has hydroxyl groups in its structure, for it is able to form both esters and ethers with various acids and alcohols respectively. When a mixture of nitric and sulfuric acids is allowed to react with cellulose, nitric acid esters are formed. The extent to which esterification takes place depends on the concentration of the reagents, the temperature, time, etc., and the "nitrocellulose" formed varies in composition accordingly. That which is used extensively in pyroxylin lacquers contains about 11.5 per cent nitrogen. *Gun cotton* is more highly esterified, contains nearly 14 per cent nitrogen and corresponds approximately in analysis to a *trinitrate* (calculated on the basis of the empirical formula $C_6H_{10}O_5$). All of the nitrocelluloses are highly flammable.

Cellulose acetate is made by causing cellulose to react with acetic acid and acetic anhydride, and is technically important in the manufacture of rayons, nonflammable photographic films and plastics. Esters of other fatty acids can be prepared such as the butyrate, laurate and stearate and find use in plastics.

The ethers of cellulose are made by treating the cellulose first with concentrated sodium hydroxide and then with alkyl (or other) halides. The most important ethers are ethyl cellulose, methyl cellulose, butyl cellulose and benzyl ($C_6H_5CH_2-$) cellulose. These have properties somewhat similar to the esters, but have the advantage for some purposes of being more resistant to water, acids and alkalis. They are used increasingly in various cellulose plastics and lacquers.

Structures of the Polysaccharides. This is a subject on which much advance has been made in recent years, especially since the subject has been studied from the analytical, synthetic and physical-chemical standpoints. We can only sketch briefly the main conclusions and cite even more briefly some of the main lines of evidence.

It has often been suggested that starch (or cellulose) consists of polymerized units, held together in some unknown fashion by secondary valence forces. These proposed units were glucose anhydrides of various types with definite complete structures represented by the formulas $C_6H_{10}O_5$, $C_{12}H_{20}O_{10}$, $C_{18}H_{30}O_{15}$ or $C_{24}H_{40}O_{20}$. This idea has been rendered untenable in the light of more recent advances.

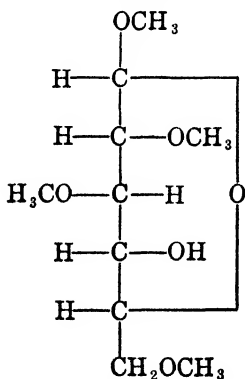
The main facts as they appear at present may be listed as follows:

1. The polysaccharides in general have structures corresponding to chains of simple sugar residues linked together in glucosidic combinations. In the case of starch and glycogen the union is α -glucosidic while in cellulose there is a series of β -glucoside combinations.

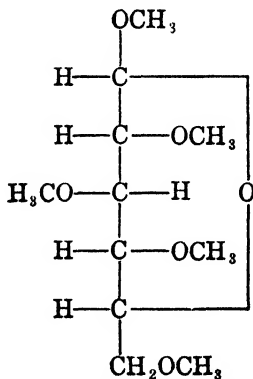
2. Probably none of the ordinary polysaccharides is homogeneous. That is, they do not consist of molecules all of the same size, but rather of a mixture of substances of varying molecular size. Any "molecular weight" which may be cited is then an approximate mean value.

3. In cellulose there are 100-200 residues linked together and the "molecular weight" is therefore from 15,000 to 30,000. In starch and inulin the number of residues is about 30 (mol. wt. ca. 5,000) and in glycogen about 12 with molecular weight about 2,000.

Chemical Evidence, Analytical. If starch or cellulose is first completely methylated (p. 172) then hydrolyzed, and finally the products treated with methanol under such conditions as to bring about glucoside formation (p. 344), 2, 3, 6, trimethyl methyl glucoside is the principal product but there is a certain amount (which differs in the two cases) of 2, 3, 4, 6 tetramethyl methyl glucoside.



2, 3, 6, Trimethyl
methyl glucoside

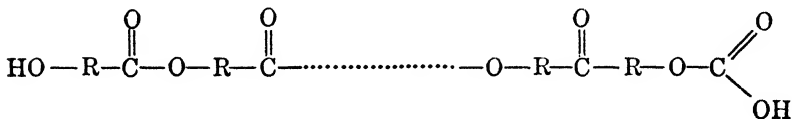


2, 3, 4, 6, Tetramethyl
methyl glucoside

The hydroxyl group in position 4 is evidently the one which was involved when the residues were linked together, but in the polysaccharide there was an end to the chain where this hydroxyl group was free. In a certain proportion of the residues therefore this position became methylated in the original polysaccharide. By determination of the amount of this 2, 3, 4, 6 tetramethyl methyl glucoside in the final mixture prepared as indicated, the length of the chain can be calculated. Similar results of limited reliability can be obtained by special methods for determining the free (potential) aldehyde groups in polysaccharides.

The lack of homogeneity of the polysaccharides is evidenced by the fact that the products of complete methylation can be separated into different fractions which yield different amounts of the tetramethyl substituted glucoside when treated separately after the manner indicated above.

Synthetic Evidence. Largely through the work of Staudinger in Germany and particularly Carothers and his co-workers in this country, high molecular weight substances of various *known* types have been built up which somewhat indirectly throw much light on the structure of the polysaccharides. These "polymerized" esters, anhydrides, etc., are prepared in such a way and behave in such a manner as to leave little doubt that they constitute long chains (molecular weights up to 20,000 or more) with open ends as indicated below. In the case of esters the free carboxyl group can in some cases be titrated satisfactorily.



These "superpolymeric" substances, like the polysaccharides, are not homogeneous, their "molecular weights" are mean values. So many different types have been prepared and their properties fall in line so excellently with what should be expected (on the basis of the polysaccharide chain structures) that they constitute convincing evidence of the fundamental soundness of the polysaccharide formulations as outlined above. The ability to be spun into continuous fibers seems to depend for one thing upon the length of the molecules. To have useful strength and pliability the constituent molecules must have a weight in the neighborhood of 12,000 and a length of at least 1000Å (.0001 mm.). A *spherical* object with this *diameter* (its mass would be much larger) would be easily visible under high magnification. These molecules are of course thread like and invisible. In order for a fiber to be strong and pliable it is necessary that the molecules crystallize or at least become oriented so that the long molecules are stretched out and run parallel to the axis of the fiber.

The fact that cellulose is the only one of the polysaccharides mentioned which is capable of existing in the form of strong fibers, is explained by the fact that in its case, only, are the molecules long enough. Long molecules tend toward strength of a fiber for the same reason that long fibers increase the strength of a thread. Many molecules lie side by side in the fiber and the fact that they overlap widely makes it difficult to break the bundle by tension. X-ray examination of cellulose fibers show patterns which indicate the presence of repeated small units. This was previously taken to indicate the presence of the

polymerized "units" mentioned above, but can as readily be interpreted as due to the presence of glucose residues which are linked together by ordinary covalence bonds. It may be stated that the available X-ray evidence concerning the polysaccharides and the analogous synthetic products indicates that the chains are fundamentally alike, and supports the idea concerning structure which are set forth above. Synthetic polymers do not show a "point diagram" indicative of an oriented structure until they are spun into fibers.

Rayon. The methods for manufacturing *rayon*, formerly called *artificial silk*, involve dissolving cellulose (wood pulp, cotton linters, etc.) and then extruding the solution through fine holes (spinneret) into a solution which causes the precipitation of the cellulose, or modified product, in the form of fine fibers.

Several methods have been employed for bringing cellulose into solution in order that it may be precipitated in the form of threads. The earliest method involved converting cellulose into nitric acid esters. Other methods which are now in use involve (1) dissolving it in ammoniacal copper hydroxide solution, (2) converting the cellulose into its acetic acid esters or (3) converting it into xanthates by the use of carbon disulfide and alkali. The latter two methods are of much greater importance.

The lower nitrates of cellulose are soluble in a mixture of alcohol and ether, and the material in this form is known as *collodion*. Such a solution may be forced through very fine openings into water which precipitates the nitrocelluloses. The nitrated cellulose may then be "de-nitrated" by a hydrolysis which converts the material back into cellulose-like material. This was one of the earliest methods of making what was called "artificial silk" but is not used at present.

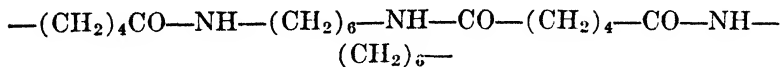
Cellulose can be made to dissolve in an ammoniacal copper hydroxide solution which is known as *Schweitzer's reagent*. The copper hydroxide causes the solution of the cellulose, by reacting with the alcoholic groups of the cellulose, to form a soluble substance. The reaction and the consequent solution of the cellulose will not take place unless there is much copper hydroxide in solution. When the cellulose solution so obtained is forced through very fine openings into an acid solution, the copper hydroxide reacts with the acid and leaves the cellulose free. The cellulose

is thus precipitated in the form of fine continuous threads. The composition of the material is essentially the same as cotton but it has the appearance of silk. Silk itself is protein in nature, and hence is quite different in chemical composition.

When cellulose acetate is dissolved in suitable solvents and the solution is forced through fine openings and the solvent is allowed to evaporate, fibers of cellulose acetate are formed. Since this material is relatively non-inflammable it may be used directly for rayon (celanese).

Another method of importance for preparing rayon involves treating the cellulose with sodium hydroxide and carbon disulfide. Sodium cellulosate is first formed by the interaction of the sodium hydroxide with the acidic cellulose, and this adds to carbon disulfide just as sodium or potassium ethylate does (p. 224). The cellulose is, by these reactions, brought into solution in water, in the form of a thick solution which is called "*viscose*." When this viscose is extruded through very fine openings into a solution of sodium bisulfate (acid in reaction), it is reconverted into cellulose. The solution is forced through a group of openings about .1 mm. in diameter; the number of openings vary from about 10 to 15 depending on the size of thread to be made. By forcing viscose through a narrow slot into the acid solution a thin film is formed. This is *cellophane*, which may be water-proofed and dyed if desired.

Nylon, Vinyon, etc. A recent outstanding development has been the production of *nylon* fibers by the du Pont Company. This material is made by the condensation polymerization of diamines such as 1,6-hexamethylenediamine with diacids such as adipic acid, and hence has a "polypeptide" structure bearing a resemblance to that of proteins, as indicated below:



The necessary diamines and diacids are produced indirectly from phenol (p. 476), and the nylon produced has found application as a substitute for silk (hosiery, etc.) and other natural fibers (as in toothbrushes). Another synthetic fiber entirely different

from rayon is *vinylon* which has been produced by the Carbide and Carbon Chemicals Company, and is apparently a copolymer of vinyl chloride and vinyl acetate. These fibers have no chemical relationship to cellulose fibers such as cotton and rayon.

Besides these developments, there have been the production of improved threads derived from cellulose as well as from natural proteins such as casein and soybean protein, and also from glass.

Explosives, Lacquers, Plastics. Aside from its use in textiles and paper, cellulose is highly important because of the uses to which its derivatives are put.

When gun cotton is in a compact mass it explodes rapidly. When treated with acetone or other appropriate solvent it swells to form a jellylike mass, which upon evaporation of the solvent is less compact and explodes less rapidly and is suitable for use in guns. The rate of explosion of this *smokeless powder* depends in part upon the size, shape (and perforations) of the powder granules.

Less highly nitrated cellulose is used as an ingredient of "pyroxylin" lacquers such as are used for automobile finishes (Duco, for example). The manufacture of such lacquers for a great variety of uses has grown into a large industry. Other cellulose esters such as the acetate, etc., and the ethers such as benzyl cellulose are also used in the manufacture of these finishes and the closely related plastics. Artificial leathers and dope for fabric covered airplane wings are important examples of applications of cellulose lacquers.

A lacquer such as is used for automobile finishing is usually a mixture of nitrocellulose (or similar) base, resins and plasticizers, pigments and solvents. The ingredients are dissolved separately and mixed into a viscous product which is diluted with thinner before use. The resins are introduced because by their use the amount of more expensive nitrocellulose can be reduced and at the same time a satisfactory product is obtained. A much used resin is "ester gum" which is made by esterifying the various acids (abietic, etc.) present in rosin with glycerol. Synthetic resins for this purpose include glyptal resins made from glycerol and phthalic anhydride (p. 517) and "vinylite"

and formaldehyde resins (polymerized vinyl and formaldehyde derivatives respectively). Some resins are limited in their usefulness by their price.

The plasticizers are used to give the film more of a plastic (and elastic) consistency and prevents contraction and checking of the film on evaporation of the solvents. Camphor was one of the earliest plasticizers used. Castor oil is another natural product used for this purpose. An increasing number of synthetic plasticizers are available for use. Among these are tri *o*-cresyl phosphate $(\text{CH}_3\text{C}_6\text{H}_4)_3\text{PO}_4$ and dibutyl phthalate $\text{C}_6\text{H}_4(\text{COOC}_4\text{H}_9)_2$. In case certain higher cellulose esters are used, lacquers can be made without the use of a separate plasticizer.

Solvents for the resins and plasticizers are not usually the best for cellulose esters. The advantage of some of the newer solvents mentioned in Chapter XV is the fact that they will dissolve many types of ingredients or will mix with solvents for different types. The solvents used are chosen for their solvent power, compatibility with other solvents to be used, evaporation rate and cheapness. Especially the thinner which is used in quantity must be a cheap solvent (mixture) and the other solvents used must be compatible with it. For applying a lacquer a number of coats are sprayed on. These vary in composition, particularly with respect to the proportions of cellulose ester, resin and plasticizer.

The cellulose plastics have much in common with the lacquers. The oldest material of this sort is celluloid which is made by compounding "nitrocellulose" with camphor. Camphor in this case acts as a plasticizer. Numerous "substitutes" for camphor may be used and numerous types of modified "molding compounds" can be made which are suitable for the fabrication of miscellaneous articles of all descriptions. Cellulose acetate and benzyl cellulose are finding increased use in the manufacture of plastics, and nitrocellulose is becoming less important for this purpose.

Other Colloidal Polysaccharides. A number of other colloidal carbohydrates occur naturally and have some importance. Agar agar, or simply *agar*, is a carbohydrate substance obtained from several varieties of sea weed especially in the Orient. It hydrolyzes to give galactose. *Gum arabic* is a mixture of salts of

a very complex acid which on hydrolysis produces arabinose. *Pectins* are colloidal carbohydrates which are found in various fruits and are used in making jellies since a very dilute solution of a pectin forms a jelly on cooling.

Glucosides. A number of substances which could hardly be classed as carbohydrates nevertheless hydrolyze to give (in part) glucose or some other simple sugar. Substances of this kind are called glucosides.

Amygdalin occurs in the seeds of bitter almonds, in peaches and in other fruit seeds. By enzyme action (emulsion) or by the action of dilute acids it is converted into glucose, hydrocyanic acid and benzaldehyde (C_6H_5CHO).

Sinigrin is a glucoside which occurs in mustard seed. When hydrolyzed it produces glucose, allyl isothiocyanate, and potassium acid sulfate.

Arbutin occurs in the leaves of the bear-berry, and hydrolyzes by boiling with water into glucose and hydroquinone, $C_6H_4(OH)_2$. These are but a few examples of a large number of known glucosides.⁹

PROBLEMS

1. What would be the relative efficiency of a glucose syrup containing 50 per cent glucose, compared with glycol, in lowering the freezing point of water in automobile radiators?

2. Must all disaccharides necessarily have 12 carbon atoms per molecule?

3. Calculate the amount of acetyl chloride necessary to completely acetylate one grain of crystalline glucose ($C_6H_{12}O_6 \cdot H_2O$).

4. What example of a "keto-triose" is mentioned in the discussion of synthesis of simple sugars?

5. Write the configuration formula for a tetrose which on oxidation would produce an optically active dicarboxylic acid.

6. Suppose that 50 ml. of a solution containing 4 grams of sucrose is allowed to ferment, what is the amount of carbon dioxide, measured at standard conditions, which will be liberated, provided the reaction goes according to the simple equation given?

7. Determine the number of stable structural isomers (not stereoisomers) of rhamnose which could exist, each with five alcohol groups and one aldehyde group.

⁹ Consult E. F. Armstrong, "The Carbohydrates and the Glucosides," Longmans, Green & Co.

8. In view of the fact that wool is protein in nature while cotton is cellulose, devise a method of distinguishing pure wool from a cotton and wool mixture, using only one reagent, namely, sodium hydroxide.

9. Supposing that enzymes are true catalytic agents, do they hasten a hydrolysis and hinder the reverse reaction? What would be the necessary condition with respect to concentration of glucose in order to favor the synthesis of maltose in the presence of an enzyme? (This result has actually been accomplished using emulsion as the enzyme.) What difficulty is encountered in attempting to produce sucrose by the action of invertase?

10. Assuming that glycogen molecules are made up of 12 residues, calculate the percentage of C, H and O. Compare with the values for $C_6H_{10}O_5$.

11. Suppose there are only two forms of glucose, one (*a*) with a specific rotation of 109.6° and the other (*b*) with a specific rotation of 20.5° . The equilibrium mixture has a specific rotation of 52.06° . In what proportions are the two constituents at equilibrium?

12. If starch were composed of triglucose anhydride units held together by secondary valence forces, what type of products would it yield by methylation and hydrolysis?

13. Suppose a preparation in dilute solution possesses enzymatic activity, but fails to give the color reactions of a protein. Does this prove that the active enzyme is not a protein?

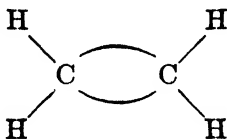
CHAPTER XXII

CYCLOPARAFFINS, TERPENES AND CAMPHORS

Cyclic (sī'klīk) structures have already been encountered from time to time in the inner anhydrides, esters, ethers, imides, etc. In all of these compounds oxygen or nitrogen atoms are in the ring in addition to carbon. We shall now be concerned with *carbocyclic* compounds in which carbon is the only element in the rings. In the present chapter only the *alicyclic* (aliphatic cyclic) compounds, as distinguished from the so-called "*aromatic*" compounds, are to be considered. The unique features of the aromatic compounds which set them apart as a separate class for study will be discussed in the next chapter.

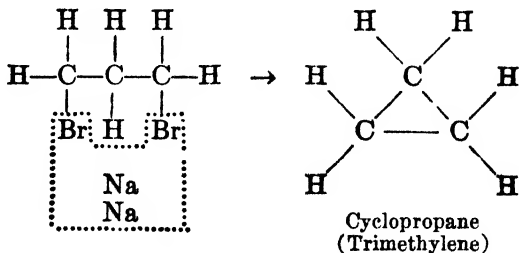
Cycloparaffins or Polymethylenes

If we separate in our minds the two valences of the double bond in ethylene



we may consider ethylene as the simplest possible carbocyclic compound. It may be designated as dimethylene or cycloethane.

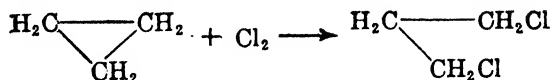
When 1,3-dibromopropane is treated with metallic sodium, a reaction of the Wurtz type takes place and one of the products is a carbocyclic compound with three members in the ring.



The compound is called cyclopropane and is used as an anesthetic.

In a similar manner cyclobutane (tetramethylene), cyclopentane (pentamethylene), cyclohexane (hexamethylene), cycloheptane (heptamethylene), etc., can be prepared. The same compounds can be prepared in other ways, some of which will be mentioned in our later discussion. These compounds form a homologous series with the type formula C_nH_{2n} which is the same as that of the olefins.

Stability of Rings. The most striking fact about this series of hydrocarbons is that unlike homologous series previously studied they do not show a great similarity in behavior. Cyclopropane acts with chlorine and bromine by addition, similar to ethylene though not so vigorously. The reaction in which the ring is broken is pictured below.



Cyclopentane and cyclohexane on the other hand behave very much like paraffin hydrocarbons and form substitution products without breaking the rings, when treated with chlorine or bromine. The behavior of cyclobutane is intermediate between that of cyclopropane and cyclopentane.

Another striking fact in connection with this hydrocarbon series is that there is not, as might be expected, a continued increase in stability as we pass to the higher members. Members higher than cyclohexane do not differ very materially in stability from this hydrocarbon. Members of the series which have numerous carbon atoms have not been studied exhaustively but recent work indicates that reasonably stable compounds can be built up with as many as thirty-two atoms in a ring. However, comparatively few compounds are known in which the rings contain more than six atoms.

Baeyer's Strain Theory.¹ In order to explain the differences in the stability of the cycloparaffins Baeyer put forth a theory

¹ A. von Baeyer (1835-1917) was an outstanding German chemist who contributed to many branches of organic chemistry. He was professor of Chemistry in the Universities of Strassburg, Munich and Berlin.

which in the main is successful. According to this theory the four valences of carbon in stable compounds such as methane, assume positions which are symmetrical with respect to each other, and the angle between any two valences in the symmetrical position is $109^{\circ} 28'$. In unsaturated compounds and in certain of the cycloparaffins, according to this theory the valences are "strained" from their normal position with the result that the compounds are unstable.

Figure I below illustrates the structure of normal pentane in which all the valences are in their normal symmetrical positions. In such cases it is assumed that there is free rotation of the different parts of the molecule around any valence axis such as *a*, *b*, *c*, or *d*.

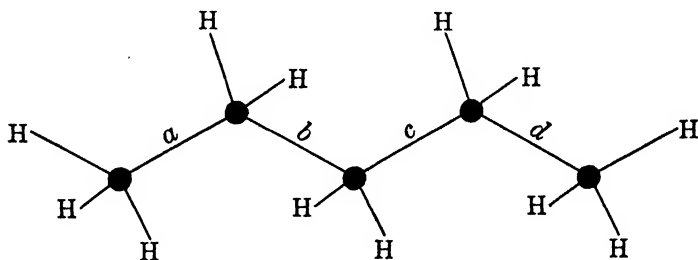


Figure I

By rotation around these axes the two terminal methyl groups can be brought close together without disturbing the normal positions of the valences. It would, therefore, be possible to close a five membered ring and obtain therefrom a stable unstrained structure.

The structure of ethylene exemplifies the idea of valences in a "strained" position. In Figure II the valences are pictured as they would exist if symmetrically arranged about each carbon atom. Figure III pictures the valences in ethylene as they are presumed to exist, in "strained positions. When this strained structure comes in contact with halogens, halogen acids, etc., one of the bonds breaks and the valences assume their normal position.

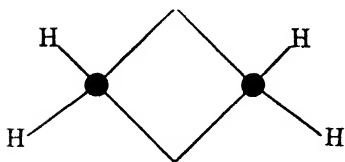


Figure II

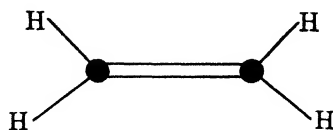


Figure III

In the case of the cyclopropane there is less "strain" from the normal positions than in ethylene. The angles between the supposed actual positions of the valences and their "normal" positions have been calculated for the different rings: ethylene, $54^{\circ} 44'$; cyclopropane, $24^{\circ} 44'$; cyclobutane, $9^{\circ} 44'$; cyclopentane, $0^{\circ} 44'$; cyclohexane, $-5^{\circ} 16'$; cycloheptane, $-9^{\circ} 33'$.

The theory predicts in a general way the properties of the various cycloparaffins, but does not predict quantitatively the relative stability of members of the series. Baeyer's theory gives a simple explanation of the fact that ring compounds with few members in the ring are invariably unstable.

The mathematical accuracy of this theory should not be stressed. It has been shown that differences in interatomic distances may modify the angles somewhat. When the formation and behavior of larger rings is interpreted on the basis of Baeyer's suggestion serious difficulties are encountered due to the fact that his calculations are based upon the assumption that the carbon atoms are all in one plane. In the larger rings this is evidently not the case and any such conception could result only from a formal consideration of molecules as rigid geometrical figures, without regard for kinetics.

Experiment has proved that rings can form when as many as thirty-two carbon atoms are involved but the closure of such a ring is difficult and results in a very poor yield because the chance of the two ends of the molecule coming within reacting distance is very small when they are separated by such a long chain. In the case of a five or six membered chain the probability of the two ends coming together (and reacting if possible) is very much higher. The higher membered rings which are neither static nor in one plane are strainless and stable like the cyclopentane ring.

The strain theory can be interpreted in terms of electronic structures. Presumably the orbits of the four electron pairs in the valence shell of carbon in saturated paraffins assume sym-

metrical positions. In ethylene and other "strained" structures these orbits are displaced from their symmetrical arrangement because of the positions of the atomic nuclei which attract them. This causes crowding and interference on the part of the electrons, and instability results.

Cis-Trans Isomerism in Ring Compounds. Whenever we have an arrangement similar to that pictured in Figure IV, *cis-trans* isomerism exists. In the figure it is the *cis* isomer that is pictured because the two A groups are in closer proximity.

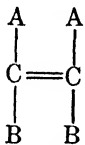


Figure IV

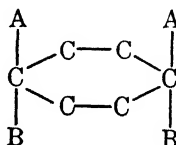


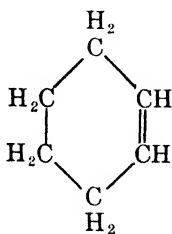
Figure V

It should be clear likewise, especially if models are used, that an arrangement such as is pictured in Figure V is one of two stereoisomeric forms, namely the *cis* form. *Cis-trans* isomerism of this type has been observed many times. There are, for example, *cis* and *trans* forms of 1,4-dihydroxy cyclohexane.

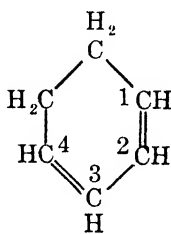
Naphthenes. The cycloparaffins and related hydrocarbons occur widely in petroleum. In Pennsylvania petroleum, for example, the lower hydrocarbons are largely paraffin in character; in the "asphalt base" petroleum, however, cyclic hydrocarbons are present, many of which are thought to be alkyl derivatives of cyclopentane and cyclohexane. It is very difficult to obtain pure hydrocarbons (except the lower ones) from petroleum and the knowledge of the individual hydrocarbons in the higher boiling petroleum fractions is scanty. Many petroleum, such as those from the mid-continent field are of a mixed type, that is they contain both paraffin hydrocarbons and cyclic hydrocarbons. Pennsylvania and Russian petroleum perhaps represent the extremes. Pennsylvania petroleum contains a minimum of cyclic hydrocarbons while some samples of Russian petroleum contain a maximum.

Unsaturated Cyclic Hydrocarbons

Unsaturated derivatives of the cycloparaffins have in many instances been prepared and a large number of such hydrocarbons are found in nature. Among the more simple unsaturated cyclic hydrocarbons are cyclohexene and cyclohexadiene which we will wish to refer to later.



Cyclohexene



Cyclohexadiene

These compounds show no unexpected behavior; they add on halogens, halogen acids, etc., in the usual way, forming compounds identical to the halogen substitution products of the cycloparaffins. The cyclohexadiene structure contains conjugated double bonds and therefore has some tendency to add at the 1, 4 positions.

Terpenes

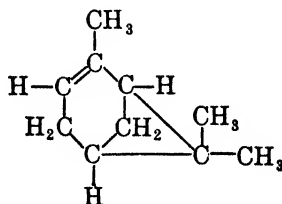
When plant tissues of various kinds, including flowers, fruits, leaves, stems, roots, hulls or rinds of fruits, are distilled with steam, volatile oils are obtained. These are very complex mixtures and are different for different varieties of plants and different tissues of the same plant.

These "essential oils" often contain substances with very characteristic odors and flavors which may be used as flavoring matter or in perfumery. These are generally oxygen compounds; esters, unsaturated aldehydes, higher ketones, ethers, etc. A few of these have already been mentioned (p. 171) and others will be described later. However, cyclic hydrocarbons which do not have especially distinctive odors often make up the major portion of the essential oils and the characteristic flavoring matters often

constitute a very small proportion of the total oil. These cyclic hydrocarbons are known as terpenes and most of them are isomeric compounds with the molecular formula $C_{10}H_{16}$. Some closely related hydrocarbons have the formulas $C_{10}H_{18}$ and $C_{10}H_{20}$.

Pinene, $C_{10}H_{16}$, is one of the most important terpenes and is the chief constituent of oil of turpentine. It also occurs very widely in plant tissues being found in such diverse essential oils as oil of rosemary, oil of nutmeg and oil of spearmint. The sap of coniferous trees is separated by distillation into two parts; the volatile part is *oil of turpentine* and the non-volatile part is *rosin* or *colophony*. Rosin contains a mixture of acids of which abietic acid (p. 404) is one. Oil of turpentine is not pure pinene or any other single substance but a complex mixture. There are different types of turpentine depending on the kind of trees from which it is obtained and the method of manufacture.

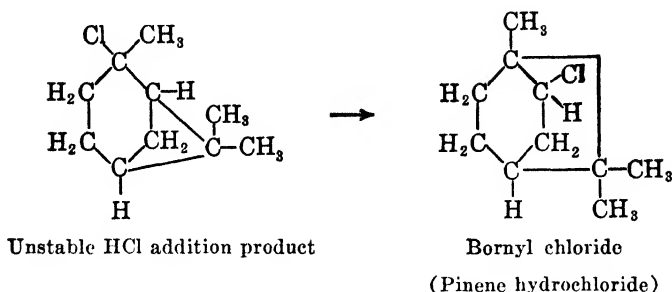
Pinene is an unsaturated cyclic hydrocarbon (b.p. 155°), which has been shown to have the following structure.



Pinene

Evidence for this structure requires too much space to give in detail here. One point, which helps in determining the structure, is that it is easily converted into cymene, *p*-isopropyltoluene (p. 419). This transformation involves breaking the four-membered ring. α -Pinene acts as a typical unsaturated compound.

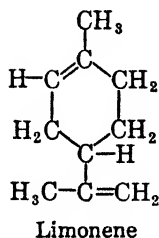
As indicated in the formula there are two asymmetric carbon atoms, and the substance exists in optically active forms. There is an unsaturated six-membered ring and a cyclobutane ring in its structure. It adds a molecule of hydrochloric acid at the double bond, after which a rearrangement takes place and a more stable cyclopentane ring is formed.



The product of these reactions is properly called *bornyl chloride* for it is the hydrochloric acid ester of an alcohol *borneol* to be mentioned later. It has been called *pinene hydrochloride* because of its origin and *artificial camphor* because it resembles camphor in odor.

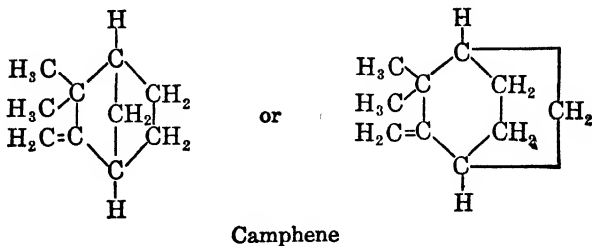
Limonene is another widely occurring terpene which is isomeric with pinene. It gets its name from its occurrence in the rind of lemons, but is also found in other sources. It has an asymmetric carbon atom in its structure and exists in nature in *dextro* and *levo* forms and as an inactive mixture. The kind that is in lemon and orange oil and oil of bergamot is the *dextro* variety. Limonene also occurs in oils obtained from pine needles and pine cones.

Limonene adds on directly two molecules of a halogen acid and can be converted into cymene. These facts and many others indicate that limonene has the structure represented below. One of the carbon atoms in the ring is asymmetric, which is in accord with the existence of optically active forms.

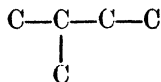


Camphene is another isomeric terpene. It is a solid, which, however, boils at 160°. It is found in a number of oils, including

the oil of lemons. It is thought to have the structure represented by either of the following two equivalent formulas.



Higher Terpenes. It may be noted by the examination of the structural formulas given for the terpenes that the skeleton structure of isoprene (p. 57), indicated below



appears twice in each formula. Not only are the molecular formulas of these compounds double that of isoprene (C_5H_8) but the structural formulas can easily be constructed using two isoprene residues as a basis. This relationship is further borne out by the existence of a series of *sesquiterpenes* $\text{C}_{15}\text{H}_{24}$, in which the isoprene skeleton appears three times, and colloidal *polyterpenes* $(\text{C}_5\text{H}_8)_n$ which are made up of a large number of isoprene residues.

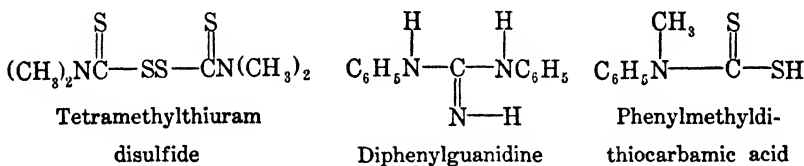
Caoutchouc or pure rubber is the coagulated latex² of certain tropical trees. Many plants yield material of the same general character, but only a few varieties yield a commercially important product. From this coagulated juice there can be obtained by the use of solvents a hydrocarbon which has been crystallized at low temperature, and which is thought to be a reasonably pure compound. Its analysis leads to the empirical

² Certain plants have so-called latex systems of communicating ducts which carry a milky fluid or latex. Its function is for the most part unknown. Other means are present in the same plants for transporting ordinary food materials and water.

C_5H_8 , and since it has a high molecular weight and yields some dipentene (*l* limonene) and isoprene on distillation it is designated as a polyterpene.

This polyterpene which is the principal constituent of rubber has unsaturated properties and forms compounds with bromine and hydrogen chloride which have the empirical formulas, $C_5H_8Br_2$ and C_5H_9Cl , respectively. The pure hydrocarbon becomes stick at body temperature or above and loses its elasticity if cooled to 0° .

Rubber shows unsaturated properties toward sulfur with which, under proper conditions, it combines. The amount of sulfur which may be taken up by the rubber in vulcanizing may be as low as 5 per cent for soft rubber up to 30 per cent for ebonite or vulcanite. In practical operations the reaction with sulfur is greatly hastened by substances which act as *accelerators*. Among the important accelerators are thiocarbanilide (p. 453) hexamethylenetetramine (p. 98), tetramethylthiuram disulfide (Tuads), zinc dimethyldithiocarbamate (Zimate), diphenylguanidine and phenylmethylthiocarbamic acid.

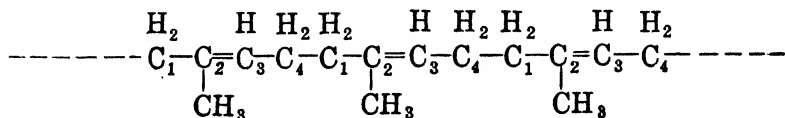


Because rubber is an unsaturated hydrocarbon, it is attacked by atmospheric oxygen quite readily. This oxidation results in a rapid loss of elasticity and strength and presents a serious problem in the utilization of rubber. The discovery that air oxidation could be retarded by certain catalysts called *antioxidants* (p. 487) was a very important advance in rubber technology. Effective antioxidants for rubber are various aromatic amines (p. 448), phenols (p. 487) and quinones. Only about 1-3 per cent of an antioxidant is sufficient to prolong greatly the life of a rubber tire.

Rubber which is used for different purposes is treated in different manners and is "compounded" with various materials

which are generally inert, such as carbon black, barium sulfate, silica, zinc oxide, etc. These fillers increase its adaptability for certain purposes as well as make possible the saving of expensive rubber. Zinc oxide also has the property of increasing the effectiveness of the accelerator and gives a finished rubber with superior physical properties.

Structure of Rubber Hydrocarbon. The methods of breaking down of rubber hydrocarbon indicate that it is made up of isoprene units. Like the polysaccharides it is probably not homogeneous, that is, it is composed of molecules of different size, but all evidence points to the probability that typical molecules are made up of approximately one thousand isoprene residues linked by ordinary valences as indicated below.



The X-ray diffraction pattern indicates an "identity period" of about 5Å (corresponding to an isoprene residue), which then makes the whole rubber molecule when extended about 0.5 micron long. This is about five times the length of an extended cellulose molecule (p. 377).

It will be noted that the linkages between the isoprene residues is represented above as between the first and fourth carbon atoms of these residues rather than by indiscriminant 1-1, 4-4 and 1-4 unions. In natural rubber it is thought partly on the basis of X-ray evidence that the linkages are regular (with a methyl group attached to every fourth atom in the chain) but that in artificial rubber made from isoprene, the polymerization takes place in an irregular manner with the result that 1-1 and 4-4 unions are present also.

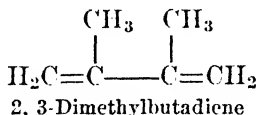
Synthetic Rubbers. For many years research has been directed toward the production of synthetic rubber-like materials or elastoprenes (elastoplastics) which could compete with natural rubber in its many uses, especially for the manufacture of automobile tires, the single largest use of rubber. This research on synthetic rubber was stimulated in Germany during World War I when they were cut off from trade with the outside world and again throughout the world in 1925 when certain artificial restrictions caused the price of natural rubber to go to

exorbitant heights. All the knowledge obtained during these periods of active research served as background for the remarkable development of a number of rubber substitutes during World War II when all warring nations with the exception of Japan were without sources of natural rubber. Several of these rubbers can even compete successfully with natural rubber in the manufacture of tires.

It should be noted that to produce a rubber-like material it is not necessary to duplicate or even approximate the chemical structure of natural rubber. In fact, only a very small amount of true rubber (*i.e.*, the naturally occurring substance) has ever been produced synthetically. The term "synthetic rubber" can be misleading, but will be used because of its wide acceptance. Only a few of the many different synthetic rubbers can be mentioned here. These rubbers will be discussed under the heading of their most important monomeric starting material.

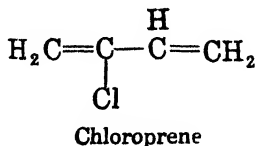
Isoprene (p. 57) which is obtained in small amounts by the distillation of rubber can be made to polymerize to yield a product which resembles natural rubber. This artificial product can be vulcanized and handled like rubber but is not identical to it.

During World War I German manufacturers made a synthetic rubber (methyl rubber) which was a useful substitute, by the polymerization of a homolog of isoprene with the formula:



This substance was made from acetone (see pinacol, p. 117).

Chloroprene. Vinyl acetylene in the presence of cuprous and ammonium chlorides (p. 62) adds hydrogen chloride to produce as one of the principal products *chloroprene* with the formula indicated.

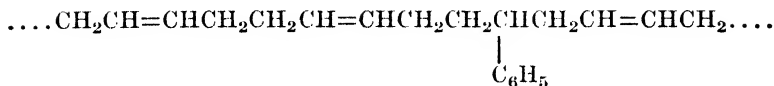


This substance is analogous in structure to isoprene except for the presence of a chlorine atom in place of the methyl group. Chloroprene polymerizes much more readily than isoprene, to produce (if the process is stopped at the right point) a product resembling natural rubber more closely than previous synthetic rubbers. By heating, it becomes vulcanized (without the use of sulfur or sulfur compounds) to produce a material (Neoprene) with the desirable properties of vulcanized rubber. Neoprene was the first synthetic rubber produced in the United States (1931). For some purposes it has definite advantages over ordinary rubber especially with regard to its resistance toward oils and hydrocarbon solvents.

It is interesting that X-ray studies of this rubber indicate that it is very much like natural rubber in structure, and is relatively free from irregularities in structure. It appears that the presence of chlorine gives the chloroprene molecule a polarity such that the addition of the molecules (polymerization) takes place in a definite way yielding a product with a regular structure. This is probably an important factor in making chloroprene rubber such a desirable material.

Butadiene. Because it was apparent that conjugated dienes of the butadiene type (isoprene and chloroprene) could be caused to polymerize in long molecules with rubber-like characteristics, the next step was to use the simplest and most easily produced conjugated diene, butadiene (p. 57). The early work on the polymerization of butadiene was done in Germany with the production of a product called Buna rubber. The butadiene was produced from acetylene through acetaldehyde and aldol. Buna rubber was not suitable for tires.

Shortly before and during World War II there was developed in the United States a method (emulsion polymerization) for co- or interpolymerization of butadiene with a second component, usually a conjugated unsaturated compound of a type different from butadiene. A mixture of about 75 per cent butadiene and 25 per cent *styrene*, $C_6H_5CH=CH_2$ (p. 420), produces a synthetic rubber (GR-S) which is at least as good as natural rubber for tire treads and mechanical rubber goods. The product is not a mechanical mixture, for the styrene is actually incorporated into the chains.



The chains are also cross-linked to some extent. Approximately 800,000 tons of GR-S rubber were produced in 1946.

The mixed polymer of butadiene and *acrylonitrile*, $\text{CH}_2=\text{CHC}\equiv\text{N}$ (p. 201), has also been produced in large quantities. This synthetic rubber can be vulcanized and the resultant product has a good resistance to oils and solvents in general, and it withstands the effects of ageing, abrasion, and heat better than natural rubber. These synthetic rubbers go under several names: Perbunan, Hycar, Ameripol, Chemigum, etc.

Isobutylenc. Isobutylene will polymerize in the presence of AlCl_3 or BF_3 to produce a chemically inert, very elastic polymer which, however, cannot be vulcanized. A small amount of butadiene co-polymerized with the isobutylene gives a product which can be vulcanized. The vulcanizate is saturated (in contrast to the usual type of synthetic rubber) and shows good resistance to ageing and chemical action. About 80,000 tons of butyl rubber are produced annually with most of it being used for inner tubes because of its high air retention. These butyl rubbers are called Vistanex or Polybutene.

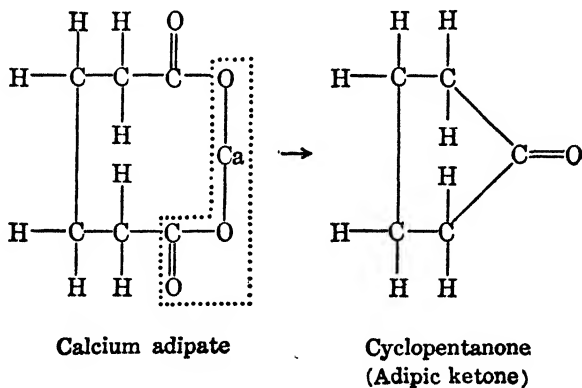
Polysulfide rubbers. The reaction between a polysulfide and a dichloride yields a type of synthetic rubber known in this country as Thiokols and in Germany as Perdurens. The two dichlorides commonly used are ethylene dichloride ($\text{ClCH}_2\text{CH}_2\text{Cl}$) and di-(β -chloroethyl) ether ($\text{ClCH}_2\text{CH}_2\text{OCH}_2\text{CH}_2\text{Cl}$). The first, with sodium polysulfide, gives Thiokol A ($-\text{CH}_2\text{CH}-\text{S}_4-$)_n and the other Thiokol B ($-\text{CH}_2\text{CH}_2-\text{O}-\text{CH}_2\text{CH}_2-\text{S}_4-$)_n. These polymers contain no ethylenic bonds and consequently they are resistant to ageing by oxygen and ozone. They are especially resistant to swelling by solvents and to abrasives.

Gutta percha is obtained from certain trees native to the Malay Peninsula. It is similar to rubber and from it a hydrocarbon can be obtained called *gutta*, which is thought to be isomeric with pure rubber. Like rubber it yields a small amount of isoprene on dry distillation. Gutta percha can be converted into

something very much like rubber but the reverse change has not been brought about.

Oxygen Derivatives of Alicyclic Hydrocarbons. Alcohols and ketones derived from the cycloparaffins are known but do not exhibit any striking properties. The alicyclic alcohol, $C_6H_{11}OH$, (hexalin) is made by hydrogenation of phenol C_6H_5OH and is important as a technical solvent and in the production of nylon (p. 379).

One method which can be used to prepare cyclic ketones is of interest. When for example calcium adipate (see adipic acid p. 249) is decomposed with heat, calcium carbonate and cyclopentanone are formed. The reaction is analogous to the formation of acetone from calcium acetate, except that it takes place between the two ends of the same molecule rather than between two molecules.



Similar reactions can be utilized to produce higher cyclic ketones, among which, ketones with as many as thirty carbon atoms to the ring have recently been obtained though in very low yields. Cyclic ketones with from 14-18 carbon atoms have the odor of *musk*. The active principle of musk itself is 3-methylcyclopentadecanone.

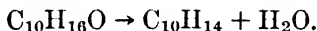
The cyclic ketones resemble ordinary ketones in their behavior. They undergo the typical addition and condensation reactions, and can be reduced to secondary alcohols which in

turn can be reduced to hydrocarbons. Like other ketones they are rather resistant to oxidation; on oxidation the ring structure breaks.

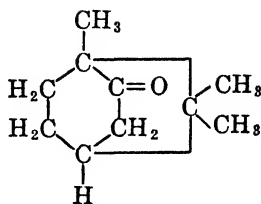
Inositol. An interesting natural occurring oxygen derivative of cyclohexane is hexahydroxycyclohexane or *inositol* (in-ō'sī-tōl). It is found in both plant and animal tissues and has the same molecular formula as the hexose sugars, $C_6H_{12}O_6$. Not having an aldehyde or ketone group in its structure, it has not the properties of a sugar. It occurs widely in nature often esterified with phosphoric acid in *phytic acid*. Recently its functioning as a vitamin has been discovered (p. 606).

Camphors and Related Compounds

Associated with terpenes are often found closely related oxygen compounds which are termed *camphors*. Ordinary camphor, $C_{10}H_{16}O$, is obtained by steam distillation of the leaves and finely chopped wood of the camphor tree. It is a solid substance, melting at 177° and boiling at 209° . In spite of its high melting and boiling points it is highly volatile at lower temperatures and has a distinct odor. It is used principally for the manufacture of celluloid, but also is used in making smokeless powder and in medicine. It has the reactions of a ketone, in that it forms an oxime, and may be reduced to a secondary alcohol. It does not form addition products with halogen acids, etc., and hence does not have doubly bonded carbon atoms in its structure. When warmed with phosphorus pentoxide it forms *cymene* (p. 419),



The problem of the determination of the structure of camphor has been a very difficult one. As many as thirty different structural formulas have at one time or another been seriously suggested to explain the properties of this substance. The complete evidence and history of the formula given below, which is now accepted, might by itself fill a good sized volume.

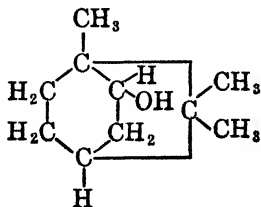


Camphor

It may be noted the skeleton formula of camphor can be constructed from two isoprene skeletons, thus showing its relationship to the terpenes.

When camphor is oxidized, oxidation takes place principally on the carbon atom already holding oxygen so that the linkage between the methylene and carbonyl group is broken and a dicarboxylic acid is formed. Camphor can be made from pinene which is obtained from turpentine, as it is closely related in structure to the product formed by the action of hydrochloric acid on pinene, the formula of which has been given. Synthetic camphor is now produced on a large scale.

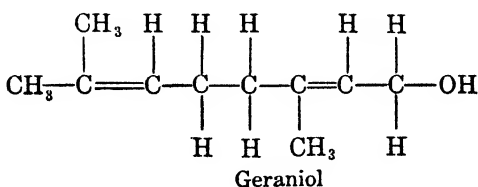
Borneol or Borneo camphor is obtained from a species of camphor tree which grows in Borneo and other East Indian islands. The product obtained from this source is *levorotatory* but the *dextrorotatory* variety also occurs naturally in some essential oils. It is an alcohol closely related chemically to camphor as the formula given below indicates. It can be obtained from camphor by reduction with metallic sodium and alcohol. Both *d*- and *l*-forms are formed in this reduction in addition to a stereoisomeric product known as *isoborneol*.



Borneol

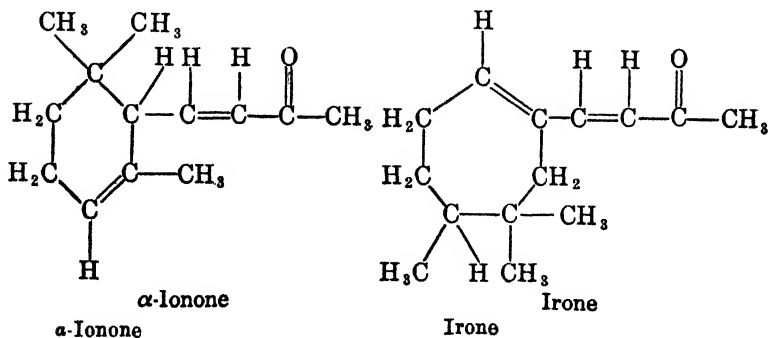
Geraniol. $C_{10}H_{18}O$, is one of three camphor-like substances (geraniol, geranial and linalool) which do not have cyclic structures and hence

should not strictly be considered at this point. However, they occur in essential oils, their formulas may all be constructed from isoprene "skeletons" and they are all easily converted into cyclic compounds which are closely related to the terpenes and camphors. Geraniol is an unsaturated primary alcohol with a rose-like odor and is the principal constituent of many rose oils, and is found in *oil of geranium*, *oil of lemon grass* and *citronella oil*. It has a high boiling point, 230°, but has appreciable vapor pressure at low temperature. It is converted into a mixture of *d*- and *l*-pinene on treatment with dilute sulfuric acid, and has been shown to have the structure:

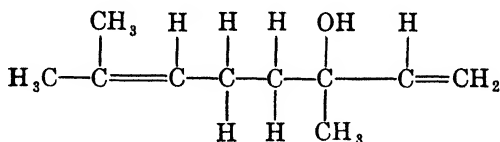


Oxidation of this primary alcohol gives the corresponding aldehyde known as *geranial* or *citral*. It is present in various oils such as that from lemon grass, geraniums, and roses. By treatment with a dehydrating agent it is converted into cymene. This reaction shows its relationship to the terpenes which are also derivatives of cymene. About a ton of citral is now produced yearly in U. S. A. for use in the perfume industry.

By condensing geranial with acetone, and treating the resulting compound with acid *α -ionone* is obtained, as one of the products. This has the odor of violets and is manufactured for use in perfumery. It is somewhat similar chemically to *irone*, which is actually present in violets. *Irone* is unusual in that it possesses a *seven* membered ring.

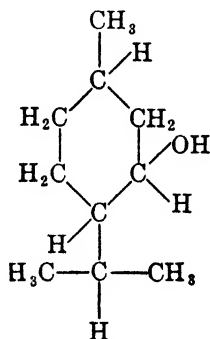


Linalool, $C_{10}H_{18}O$, is present in *oil of bergamot* and *oil of lavender*. It is isomeric with geraniol and can be converted into geraniol by the action of acids. The change consists in a shift of the positions of the hydroxyl group and of the double bond.

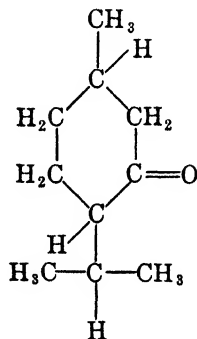


Linalool

Menthol, $C_{10}H_{19}(OH)$, is the principal constituent of *oil of peppermint*, which also contains the corresponding ketone *menthone* in smaller amount. Menthol is a crystalline substance which melts at 42° and boils at 212° . It has the odor characteristic of peppermint oil.



Menthol



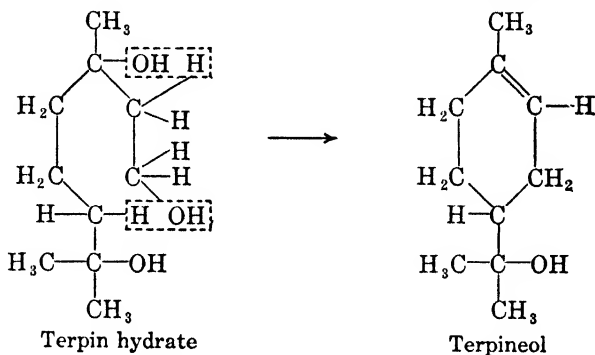
Menthone

It will be noted that menthone and menthol are related to each other in the same way as are camphor and borneol.

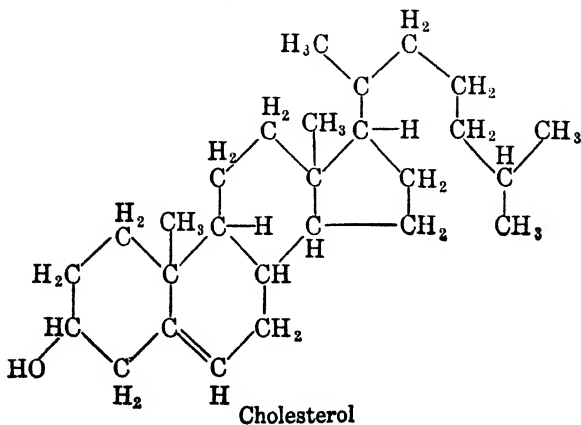
Pulegone, $C_{10}H_{16}O$, from *oil of pennyroyal*; *carvone*, $C_{10}H_{14}O$, from *oil of caraway*; *eucalyptol* (cineol), $C_{10}H_{18}O$, from *eucalyptus oil*; and *terpineol*, $C_{10}H_{18}O$, which occurs in *oil of orange*, are examples of other well-known camphor-like substances which are present in the essential oils.

Terpineol has an odor resembling that of hyacinths and lilacs and is made technically from turpentine for use in perfumes. When oil of turpentine is allowed to stand for some time with

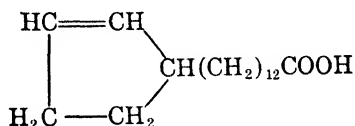
dilute sulfuric acid a substance known as *terpin hydrate*, with the structure indicated below, is formed from the pinene present. In the manufacture of commercial terpineol terpin hydrate is converted into a mixture of terpineols by dehydration.



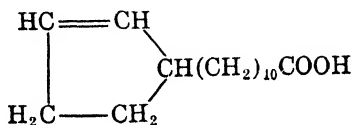
Cholesterol (kó-lēs'tēr-ōl), $C_{27}H_{45}OH$, is a very complex monohydric alcohol which is related to the terpenes in structure. It is often the chief constituent of gall stones, and is present in blood and tissues generally. It is especially abundant in brain tissue. It is thought to have important (though rather indefinitely described) functions in the body. It is chemically related to another sterol *ergosterol* (ēr-gös'tēr-ōl). Natural fats always contain more or less cholesterol as well as ergosterol. The structure of cholesterol is indicated below.



Chaulmoogric acid and **hydnocarpic acid** occur as glyceryl esters in chaulmoogra oil which has been used extensively in the treatment of leprosy. They have alicyclic rings in their structures as is shown by their formulas below:

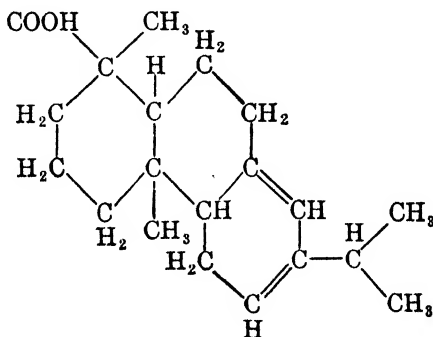


Chaulmoogric acid



Hydnocarpic acid

Abietic (ăb-ĭ-ĕt-ĭk) **acid**, $\text{C}_{20}\text{H}_{30}\text{O}_2$, is one of the prominent acids present in rosin (p. 390) and has been assigned the structure indicated below.



Abietic acid

It is a carboxylic acid derived from a diterpene $\text{C}_{20}\text{H}_{32}$, and its skeleton structure can be constructed from four isoprene "skeletons."

PROBLEMS

1. How much bromine would be taken up (a) by 0.5 gram of pinene, (b) by 2.0 gram of limonene?
 2. What other products may be formed simultaneously with cyclopropane in its synthesis from 1,3-dibromopropane?
 3. What type of compound would be produced by treating camphor with magnesium methyl iodide, and hydrolyzing the product? Which of the various compounds studied would you expect it to resemble most?
 4. Starting with calcium pimelate, show how a hydrocarbon of the cycloparaffin series can be prepared.
-
5. Why is it difficult to say with absolute certainty that a sample of purified rubber is a pure chemical compound? Are the results of an analysis conclusive evidence? Does crystallization constitute proof? Why?
 6. Assuming the correct formula for rubber is indicated and that each double bond adds one atom of sulfur during vulcanization, what would be the percentage of sulfur in a completely vulcanized product?
 7. Draw a diagram and calculate the "angle of strain" in the cyclopropane ring.
 8. Draw the structure of zinc dimethyldithiocarbamate (Zimate).

CHAPTER XXIII

BENZENE AND ITS HOMOLOGS

By the dry distillation of coal a number of volatile substances are formed of which the most important is *benzene*. This is a definite chemical substance, C_6H_6 , and must not be confused with benzine which is similar to gasoline in composition and is therefore a complex mixture. In order to avoid the confusion of having the names of two materials pronounced in the same way, the hydrocarbon C_6H_6 is commonly called "benzol" in the industries in which it is used. This is not a proper chemical name, however, since the ending *ol* is used to signify the presence of a hydroxyl group in a structure.

Benzene is an exceedingly important compound not alone because of the importance of its structural derivatives but because numerous of these derivatives are actually prepared from benzene itself. The situation is different from that which exists in the paraffin hydrocarbons, the derivatives of which are more frequently *not* made from the corresponding hydrocarbons themselves. Benzene is the parent substance of an enormous family of *aromatic* compounds. (The exact significance of the term "aromatic" will be made clear later in the chapter.) Besides these uses benzene and especially its homologs are employed extensively in motor fuels. Their "antiknock" value is high.

The derivatives of benzene and related hydrocarbons are exceedingly important especially from the standpoint of industry. They are relatively unimportant as constituents of animal and plant tissues. There are three common amino acids found in proteins which are benzene derivatives; aside from these amino acids and substances derived from them, there are relatively few tissue constituents which belong to the aromatic group of compounds.

Coal Tar as a Source of Aromatic Compounds. When coal is heated in the absence of air, decomposition takes place with

the formation of a very large number of compounds. In the early history of the distillation of soft coal the purpose of the distillation was to obtain gas for lighting purposes and coke for the manufacture of iron and steel. In this process much tar was formed, but little use was made of it. At present coke and gas are still highly important but a large number of compounds are obtained from coal tar and from the more volatile distillation products, which are indispensable to present day civilization. Among these substances are *benzene*, *toluene*, *xylenes*, *naphthalene*, *anthracene*, *phenol*, *cresols*, *pyridine*, *quinoline* and *carbazole*, all substances of the aromatic type which will be studied later. A great many derivatives of benzene have been made, among them the so-called "coal tar" dyes, and the synthetic "coal tar" drugs. These derivatives, of course, do not exist in the coal tar as is sometimes popularly supposed.

In recent years petroleum has become a potential source of benzene and other aromatic hydrocarbons because by catalytic cyclization at 500° normal hexane and closely related homologs are converted practically quantitatively into benzene and its homologs, with hydrogen as a by-product. Cresols and other phenolic compounds are also obtained from petroleum as well as from coal tar.

Distillation of Coal and Coal Tar. About one-eighth of the coal used in this country is converted into coke, primarily for metallurgical purposes. The most important method of coking is in the by-product coke ovens which are designed so that the by-products are recovered. By this method one ton of soft coal yields the following products: coke, 1400 pounds; tar, 10 gallons; ammonia, 5½ pounds; "light oil," 3 gallons; gas, 11,000 cubic feet. (Especially in England and Germany, the coking of coal, at considerably lower temperatures than formerly used, has come to be important. In this way much more of the coal is converted into liquid and gaseous products, in fact the yield of gas may be about doubled, the yield of oils is nearly doubled, and two or three times as much tar is obtained. The products are somewhat different in character. By heating powdered coal under pressure in hydrogen gas a larger yield of liquid hydrocarbons, which can be used as a source of motor fuel, is obtained. This brief discussion will be concerned with the products as they are obtained by the ordinary high temperature carbonization.)

The "light oil" and tar mentioned above are of especial interest because they are the source of many aromatic compounds. The gases which are formed in coking are first separated from the tar and ammonia and then passed through large scrubbing towers where they come in intimate contact with a stream of high boiling oil which flows counter-current to the gas. The oil used for this purpose is a petroleum distillation product. It readily dissolves the low boiling aromatic hydrocarbons present in the gas, and removes them almost completely from the gas. The "light oil" is removed from the solution by steam distillation and becomes an important source of benzene, toluene, xylene and other volatile aromatic hydrocarbons. A representative sample of this "light oil" contains about 60 per cent benzene, 15 per cent toluene, 10 per cent xylenes and light solvent naphthas, and the remainder is higher hydrocarbons, etc. A considerable amount of this light oil is partially refined and used as an ingredient of "benzol motor fuels" which consist of gasoline to which 30-50 per cent "motor benzol" is added.

Most of the coal tar from by-product coke ovens is refined at least to some extent. When it is distilled until the residue is hard pitch, the following products are obtained in the percentages indicated.¹

	Per cent
Water	1.25
Light oil (0°-170°)20
Carbolic oils (170°-230°)	9.48
Creosote oil (230°-270°)	10.08
Anthracene oil (270°-350°)	22.71
Pitch (at 350°)	56.28

These figures serve to emphasize the fact that there is very little benzene in the by-product coal tar itself as compared with that recovered from the gas. The "carbolic oil" fraction is cooled in crystallizing pans where naphthalene crystallizes out. This is removed by centrifuging and the residual oil treated with sodium hydroxide which dissolves the "tar acids." Crude carbolic acid (phenol) and cresols (cresylic acids) are obtained from this source. Naphthalene is recovered as indicated above from the "creosote oil" fraction also, and the residue mixed with that from the preceding fraction, is sold as "creosote oil" for treatment of wood that is to be buried in the ground, etc. Various grades of tar with more or less of the oils removed are used for cheap paints, for saturating roofing felts, for binders in asphalt pavements, for sprinkling roads to prevent dust, etc.

In American practice the tar is most often not distilled to hard pitch but instead the distillation is stopped at about 270° C. leaving a residue

¹ From F. F. Marquard, Yearbook of the American Iron and Steel Institute (1919).

of soft pitch which is in good demand. When this procedure is followed, the anthracene, phenanthrene and carbazole present in the "anthracene oil" fraction are not recovered.

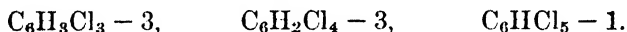
Chemical Properties of Benzene. Before considering the question of the structure of the hydrocarbon C_6H_6 , it will be well to call attention to a few outstanding facts with regard to its chemical behavior. These will serve as a basis for the discussion of the benzene structure.

1. Benzene under most conditions behaves like a saturated compound. It can be boiled for hours with permanganate without being oxidized. It furthermore forms substitution products readily with halogens, etc., in a manner which is characteristic of saturated hydrocarbons.

2. Though benzene derivatives have been prepared in many ways and studied thoroughly no one has been able to prepare more than one mono-substitution product of benzene in which a particular atom or group is substituted. In fact an elaborate series of reactions can be cited which prove that no matter which of the six hydrogen atoms is replaced the product is the same.

3. Benzene forms three isomeric di-substitution products with, for example, the formula $C_6H_4Cl_2$.

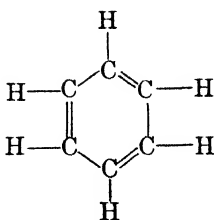
4. The number of isomeric substituted benzenes represented by formulas of the following types are as follows:



5. In the presence of light, benzene reacts with halogens by addition (as well as substitution) but does not add on halogen acids under any circumstances. Benzene can also react by addition with hydrogen at a moderate temperature in the presence of a catalyst. The final product formed by this reaction is cyclohexane (p. 386).

Kekule Structure. In 1865 Kekule² suggested the structure for benzene which is indicated below.

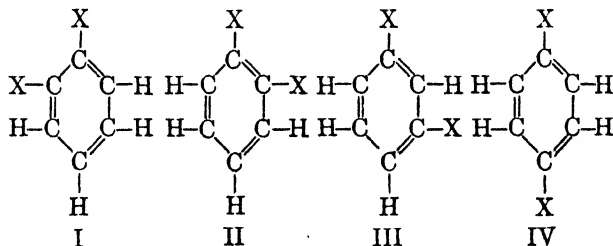
² August Kekule (1829-1896) should be remembered not only for his famous benzene structure, but also because he was probably, more than any other chemist, the father of structural organic chemistry as applied also to aliphatic compounds. He was Professor of Chemistry in Bonn, Germany.



At that time the idea of a ring structure for any compound was new and Kekule's suggestion was a tremendous step forward.

The structure represented above explains the fact that benzene enters into addition reactions, and that cyclohexane is produced by hydrogenation. If the double bonds are regarded as capable of "dormancy," the formation of substitution products is also in accord with the formula. Furthermore the symmetrical hexagon formula is in accord with the fact that no matter which hydrogen of benzene is replaced by a particular atom (chlorine for example) the same product results.

In its original form the Kekule formula would predict the existence of four (instead of three) di-substituted benzenes corresponding to the following formulas.



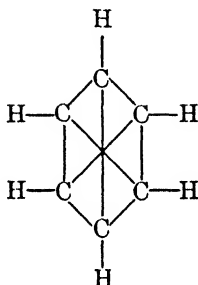
Kekule met this objection by postulating that the double bonds are constantly shifting in their position in the ring and therefore formulas I and II are identical. He thus introduced the idea of a dynamic instead of a static structure.

With this modification Kekule's structure is in accord with all the facts cited above with regard to the number of isomeric substitution products. Only simpler cases are cited above. In more complex cases where more than one kind of substituent is involved the modified Kekule formula works just as well as in the simpler cases. These facts as well as the known production of

cyclohexane by hydrogenation of benzene removes all doubt as to the validity of the hexagon ring as a formulation for benzene.

It must be admitted, however, that one must be very much prejudiced in favor of the formula to overlook the fact that benzene ordinarily behaves like a saturated compound, while the formula represents it as a highly unsaturated one.

Claus³ Formula. The benzene formula of Claus may be represented as follows:



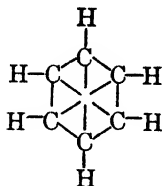
It is one of those which has been designed to dodge the weakness of the Kekule formula. In order to be a useful formula the valences across the ring in this structure must be of a different type than those in the ring. Otherwise the formula will not predict the right number of isomeric derivatives. Recently Pauling and Lucas have revived this structure in its essentials in a model which is drawn in terms of electron orbits and which has several advantages to commend it.

Centric Structure. In order to correct the weakness in the benzene structure Armstrong⁴ first proposed the centric structure and Baeyer became its chief defendant. In this formula no double bonds are pictured but one valence from each carbon atom is "directed toward a center."

³ Adolf Claus (1840-1900) was Professor of Chemistry in the University of Freiburg.

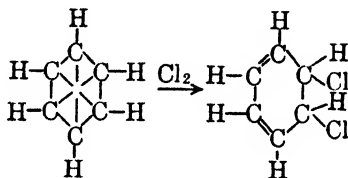
⁴ H. E. Armstrong (1848-1937) was Professor of Chemistry in the Central Technical College in London. He first suggested this formula in 1887, after which it was taken up and defended by Baeyer (p. 385) who was more widely known.

The "centric" valences were thought to be brought into play only under certain conditions in which case benzene showed unsaturated properties to some extent.



It has been cited as an argument against this formula that it introduces a new kind of valence not encountered before. From one standpoint this is not as serious a point against the formula as it might be because in benzene we actually do observe valence phenomena different from any previously encountered.

After the addition of two atoms to benzene the molecule changes, according to Baeyer, to a true unsaturated compound, as pictured below:



This is in accord with the experimental facts because after two atoms have added to benzene the resulting compounds add halogens readily, also halogen acids which do not add to benzene at all.

The centric formula does not picture why addition to benzene always takes place two atoms at a time and in 1,2 or 1,4 positions, but this is perhaps not a very serious fault.

Partial Valence Formula. The application of Thiele's idea of partial valence to Kekule's benzene formula constituted a definite step in advance. The double bonds in benzene are in positions such as to constitute a conjugated system in which there are no free residual valences. This is represented by Figure I below or better yet by Figure II.

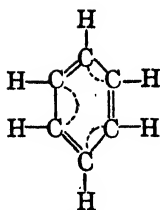


Fig. I

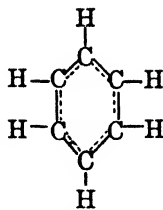


Fig. II

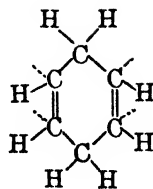
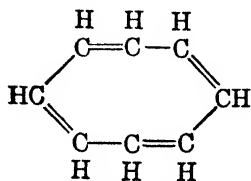


Fig. III

Figure II is preferable because if the static condition represented by Figure I existed, four dichlorobenzenes, $C_6H_4Cl_2$, for example, would exist. In such a system as we are considering there is no reason to picture any particular pair of carbon atoms as more definitely doubly bonded than any other adjacent pair.

The complete conjugation of all residual valences explains why benzene fails to act as an unsaturated compound under most conditions, and at the same time the formation of addition products under peculiar conditions is to be expected. The first addition to benzene may take place in the 1-4 positions as well as in the 1-2 positions; in the former case the product would be represented as in Figure III, and in either case the product would have free residual valences and therefore behave as a typically unsaturated compound.

The worst criticism that can be directed against the partial valence idea in this connection is that the conjugation in the case of benzene seems to be more definite and complete than in other authentic cases. In muconic acid (p. 290), for example, addition



Cyclo-octatetraene

does not take place exclusively in the 1-4 positions. The conjugated partial valences are by no means wholly inactive. Likewise cyclooctatetraene which possesses a conjugated system, does not possess the saturated character of benzene. There is some-

thing unique about the six membered ring which makes possible a very stable structure. Probably it is the fact that the normal interatomic distances and angles are such that all six carbon atoms can lie in one plane. It would appear that what would be regarded as merely a tendency in other conjugated systems becomes much more definite and striking in the case of benzene.

Space Formula. A large number of formulas for benzene have been proposed including one which pictures the carbon atoms situated at the six corners of a prism (Ladenburg) and another (Collie) which postulates the symmetrical arrangement of carbon atoms in space. On the basis of much evidence, including stereochemical and particularly that of a physical nature (X-ray, etc.) it seems certain that the carbon atoms in the benzene nucleus lie almost if not quite in one plane, and thus occupy positions corresponding to the corners of a hexagon. The distance between adjacent carbon atoms in the ring is 1.42 \AA which is about midway between the single bond distance 1.54 \AA and the double bond distance 1.34 \AA . From the standpoint of the arrangement of atoms in space and the interatomic distances, our knowledge of the structure of benzene is in a very satisfactory state.

Study of benzene structure from the standpoint of quantum mechanics (Pauling) leads to the conclusion that the following five structures represent different forms of approximately the



I



II



III



IV



V

same energy content and that the benzene structure is not represented by any one but results from resonance between the various forms, of which the first two make the largest contribution. The latter three taken together may be considered as the equivalent of the Claus formula. From the standpoint of this discussion, Kekule's dynamic model appears to have been a tremendous

stride in the right direction, especially when the Claus formula is also incorporated in it; the centric and partial valence formulas appear as valuable interpretations. The contribution of quantum mechanics appears to be the conception of a stable structure much more stable than any of the forms pictured, resulting from resonance between them.

Stability of the Benzene Nucleus. The fact that the benzene nucleus is extraordinarily stable has perhaps not been adequately stressed in the foregoing discussion. Benzene as a compound cannot be classed as unreactive, as we shall note later, but it generally reacts to form substitution products in which the ring or nucleus remains unbroken. It is possible starting with benzene to prepare thousands of derivatives without at any time breaking down the nucleus of six carbon atoms. As we shall note later the introduction of certain substituents by indirect means facilitates the breaking of the ring so that it is by no means impossible to break it.

Meaning of the Term Aromatic. The term "aromatic" was originally used to designate derivatives of benzene because of the pronounced and agreeable odor which many were known to possess. The term has been retained although it has lost its original significance. The possession of an agreeable odor is not common to nor confined to "aromatic" compounds as we now use the term. The one characteristic likeness in all aromatic compounds is the possession of a *stable ring or nucleus* such as is present in benzene.

There are several "parent" stable ring compounds like benzene; these and their derivatives along with benzene and its derivatives, constitute the group of compounds which we call "aromatic." All aromatic rings possess unsaturation in the sense that benzene does, and the derivatives have certain characteristics which are common to aromatic compounds but unlike those of the aliphatic compounds. These peculiarities of behavior will be dealt with in our further study.

Importance of Substitution Products. Whatever means is taken to represent the structure of benzene, the fact remains that

in the structure there is a stable nucleus of six carbon atoms which goes through very many reactions unscathed and breaks up only under the action of strong reagents at rather high temperatures. We shall be concerned primarily with the substitution products of benzene. In many of the transformations of these substances the six-membered nucleus is unchanged, and we are therefore little concerned with those valences which are inadequately represented by any single formula.

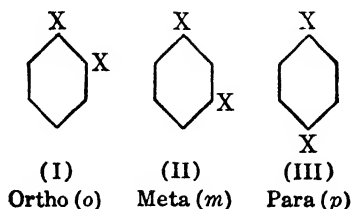
Abbreviated Formulas. For this reason it is customary to abbreviate the formula of benzene by means of a simple hexagon. The hexagon alone is used to represent benzene itself, and in the case of substitution products *only the substituted groups* are indicated. A carbon atom is understood to be situated at each corner of the hexagon, and a hydrogen atom is understood to be attached to each carbon atom unless some other atom or group is represented in its stead.



Benzene

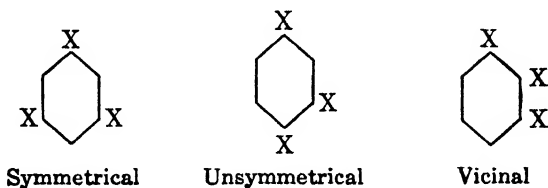
The disposition of the fourth valence of each carbon atom is disregarded. To refer to positions where substituted atoms or groups are present, the positions are numbered as indicated. As there is only one mono-chlorine substitution product, only one mono-ethyl substitution product, etc., the position of any one substituent may be represented at any place on the hexagon. The numbers are necessary only in cases where more than one hydrogen atom is replaced in the formula.

Since the di-substitution products of benzene are plentiful and important, it is convenient to designate the relative position occupied by the two substituents by name rather than by numbers. **Ortho**, **meta**, and **para** are the names applied to the three relative positions in which the two groups may be situated.



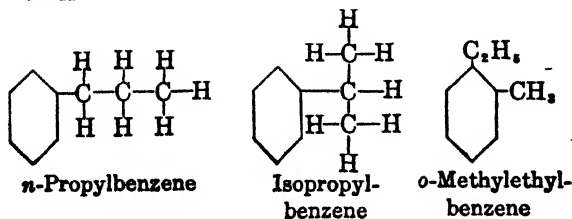
No significance is given to whether or not a group is attached to top, bottom, or to the side of the hexagon, the only significant relationship is whether or not the two groups are adjacent, have one unsubstituted position between them, or are opposite each other on the ring. The selection of the names for the different positions is largely arbitrary. The terms *ortho* and *meta* have no connection with the same terms as applied to the phosphoric acids.

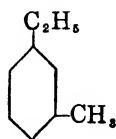
Similarly the three possible trisubstitution products of benzene are sometimes named as follows:



Homologs of Benzene

There is, in accordance with our previous discussion, only one methylbenzene, $\text{CH}_3\text{C}_6\text{H}_5$, which is known as *toluene*. There are, however, four possible structures corresponding to the molecular formula C_8H_{10} . One of these is ethylbenzene and the three others are *ortho*, *meta* and *para* dimethylbenzenes. The hydrocarbons whose structures are given below correspond to the molecular formula C_9H_{12} .

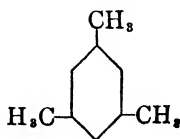




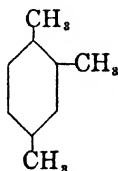
m-Methylethyl-
benzene



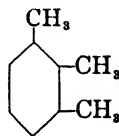
p-Methylethyl-
benzene



1, 3, 5,-Trimethyl-
benzene
(sym. trimethyl-
benzene)



1, 2, 4-Trimethyl-
benzene
(unsym. trimethyl-
benzene)



1, 2, 3-Trimethyl-
benzene
(vicinal trimethyl-
benzene)

All of these homologs of benzene are known as well as many others, but their individual discussion is not warranted. In addition, a number of derivatives of benzene are known which possess unsaturated hydrocarbon groups. They show the characteristic unsaturated behavior but are not of special interest or importance. Some of the derivatives of benzene are listed in the accompanying tables.

A number of the homologs of benzene are becoming increasingly important technically because of their availability from petroleum in large quantities at a low cost (p. 27).

Toluene (toluol) is used extensively in the lacquer industry as a solvent and diluent. It is also used in the manufacture of dyes, as a blending agent in gasoline and for the manufacture of trinitrotoluene (TNT, p. 442). The three isomeric *xylene*s (*xylol*) are used as solvents and diluents and in the preparation of various derivatives. A mixture of the isomers is used because they boil within about a 4° range and cannot be readily sepa-

rated by fractional distillation. *Cumene* (isopropylbenzene) is used as a blending agent in high octane gasoline.

Aromatic Hydrocarbons

Benzene and Homologs ⁵	Melting Point	Boiling Point	Density 20/4
Benzene, C_6H_6	5.51	80.09	.8789
Toluene, $C_6H_5CH_3$	-95.0	110.7	.8669
Xylene (<i>o</i>), $C_6H_4(CH_3)_2$	-25.0	144.5	.8801
Xylene (<i>m</i>), $C_6H_4(CH_3)_2$	-47.8	139.2	.8642
Xylene (<i>p</i>), $C_6H_4(CH_3)_2$	13.2	138.4	.8601
Triethylbenzene, $C_6H_3(C_2H_5)_3$ (sym.)	—	211.2	.8568
Ethylbenzene, $C_6H_5C_2H_5$	-95.0	136.2	.8669
Mesitylene, $C_6H_3(CH_3)_3$ (sym. trimethylbenzene)	—	164.6	.8653
Cumene, $C_6H_5CH(CH_3)_2$ (isopropylbenzene) ..	-96.1	152.4	.8615
Cymene, $C_6H_4(CH_3)C_6H_7$ (<i>p</i> -methylisopropylbenzene)	-68.8	175.0	.8644
<i>n</i> -Butylbenzene, $C_6H_5(CH_2)_3CH_3$	-88.5	182.6	.8642 (15°)
Isobutylbenzene, $C_6H_5CH_2CH(CH_3)_2$	—	170.0	.8628
Secondary butylbenzene, $C_6H_5CH(CH_3)C_2H_5$..	-82.7	171.0	.8577 (25°)
Tertiary butylbenzene, $C_6H_5C(CH_3)_3$	-58.1	167.0	.8623 (25°)
Hexamethylbenzene, $C_6(CH_3)_6$	164.8	263.8	—
Pentamethylbenzene, $C_6H(CH_3)_5$	54.0	231.9	—

Unsaturated Aromatic Hydrocarbons

Styrene, $C_6H_5CH : CH_2$	-30.6	145.2	.9056
Stilbene, $C_6H_5CH : CHC_6H_5$	124.0	306.0	1.164 (0°)
Phenylacetylene, $C_6H_5C : CH$	-40.0	141.7	.9281
Tetraphenylethylene, $(C_6H_5)_2C : C(C_6H_5)_2$ ⁶ ..	221	420	—
Tolane, $C_6H_5C : CC_6H_5$	59.0	300.0	—

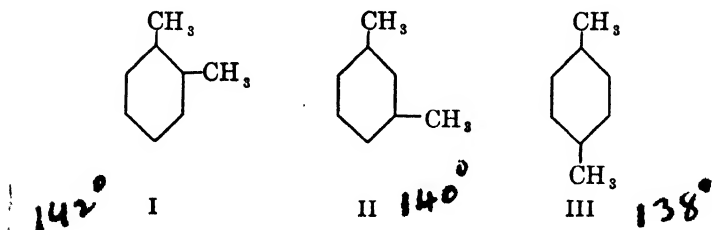
p-Cymene (*p*-methylisopropylbenzene) is an especially interesting and important hydrocarbon because it occurs in several natural oils such as oil of thyme and eucalyptus oils and many of the terpenes (p. 389) are structurally closely related to it.

⁵ Tables of this kind always include only a small fraction of the total number of known compounds. The more important compounds are generally included and the student may note numerous other possibilities.

⁶ This compound shows only weak unsaturated properties. The effect of the phenyl (C_6H_5) groups on the double bond is marked. Extraordinary valence phenomena are exhibited by compounds which are somewhat similar to this one (Chapter XXXII).

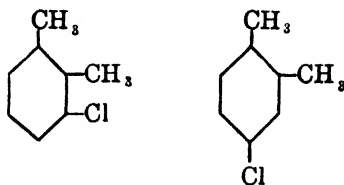
Styrene (phenylethylene) is synthesized by the alkylation of benzene with ethylene and subsequent dehydrogenation of the ethylbenzene. Styrene is used to make polystyrene resins and synthetic rubber.

Determination of the Position of Substituents. There are three isomeric dimethyl benzenes with boiling points of 138° , 140° and 142° . There are likewise three formulas:

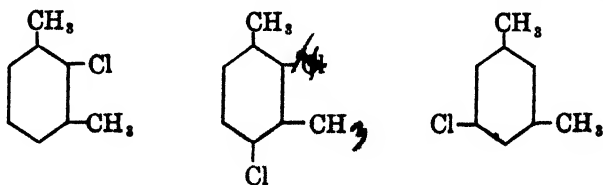


We have not yet raised the question of how we can know which structure corresponds to each of the three isomeric hydrocarbons.

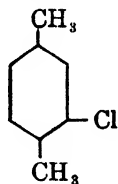
Absolute Method. By the substitution, for example, of chlorine for hydrogen on the ring in the above formulas we find that I above should theoretically yield two monochloro substitution products with the formulas:



Structure II should yield three substitution products.

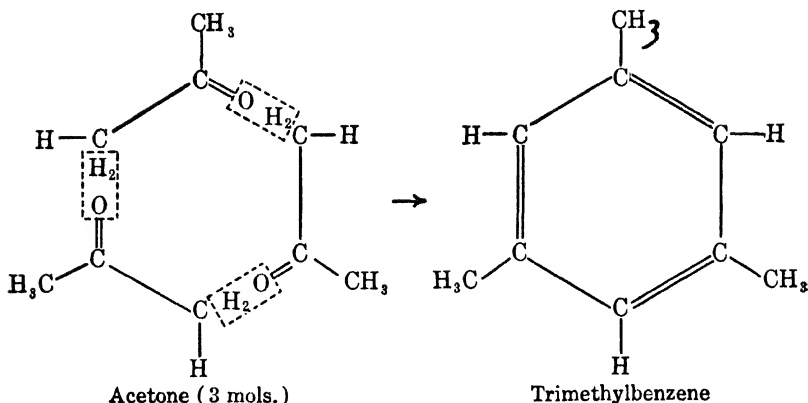


Structure III on the other hand is capable of yielding only one such substitution product.



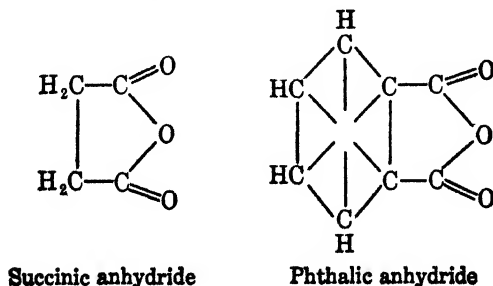
Experimentally it is found that the dimethylbenzene which boils at 138° yields only one monochloro substitution product when treated with chlorine under conditions which cause substitution to take place on the ring. The dimethylbenzene boiling at 142° yields two isomeric substitution products under similar conditions and the one boiling at 140° can be made to yield three such substitution products. Evidently, therefore, structure I (*ortho*) should be ascribed the compound boiling at 142° ; structure II (*meta*) applies to the boiling at 140° and structure III belongs to the one which boils at 138° . The experimental application of this method to particular cases is not easy because it involves the separation and perhaps analysis of the isomers, and in any event it is not always possible to cause a substituting group to take all the possible positions. The entering group may be directed quite definitely to a particular position, as will be explained later. Fortunately, however, the fundamental method outlined above does not have to be applied to each new compound, as there are easier ways of arriving at the same conclusions.

Other Lines of Evidence. Confirmatory evidence that the *meta* compound is the one boiling at 140° is derived from the following considerations. Acetone when heated with sulfuric acid to which some water has been added, yields a trimethylbenzene by loss of three molecules of water from three molecules of acetone. See reaction pictured at top of page 422. No matter how the reaction is interpreted one reaches the conclusion that it must be the symmetrical trimethylbenzene which is formed rather than the unsymmetrical or vicinal forms. This has also been proved by independent means. The trimethylbenzene so obtained can be carefully oxidized to a monocarboxylic



acid and the carboxyl group removed by heating with lime (p. 140). (Alkyl or other "side chains" attached to the benzene nucleus are characteristically oxidized to the carboxyl group p. 426.) The resulting hydrocarbon which, from its method of formation, must be the *meta* compound proves to be identical to the one which yields three isomeric products as explained in the previous section. We have therefore two proofs that the dimethylbenzene which boils at 140° is the *meta* compound.

Further proof is also available as to identity of the *ortho* compound. When the three dimethylbenzenes are strongly oxidized they yield three isomeric dicarboxylic acids called phthalic acids. One of these forms an inner anhydride readily and it is the only one which can by any means be made to form an inner anhydride. By analogy with succinic acid which also forms an inner anhydride readily one concludes that the acid which forms the anhydride must be the *ortho* compound.



By referring to our results above we find that the dimethylbenzene which boils at 142° yields by oxidation the particular acid which is capable of forming the inner anhydride. We have confirmatory evidence therefore, that it is the *ortho* compound.

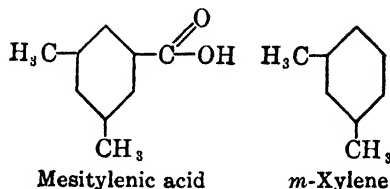
Indirect Method. Having established the structures of the three dimethylbenzenes we can use them as "reference substances" to determine the structures of other compounds which may be derived from them. It is obvious, for example, that the dicarboxylic acid derived from *meta* dimethylbenzene is the *meta* acid and the dicarboxylic acid obtained by the oxidation of the *para* hydrocarbon is the *para* acid. The three acids which can now be used as reference substances can be distinguished by the fact that the *ortho* acid forms an anhydride on heating, the *meta* acid melts at 300° and the *para* acid sublimes without melting. Suppose for example we have a sample of diethylbenzene, and wish to ascertain which one it is. It is only necessary to oxidize a sample of the hydrocarbon to a dicarboxylic acid and determine which one it is. If the acid melts at 300° the hydrocarbon is *meta*, if it sublimes without melting the hydrocarbon is *para*, if it decomposes to form an anhydride, the hydrocarbon is *ortho*.

If the dimethylbenzenes are oxidized carefully so that only one of the methyl groups is oxidized, the structures of the three resulting acids are determined by reference to the hydrocarbons from which they were obtained. These three monocarboxylic acids can then be used as reference substances. If, for example, one has a methylcyanobenzene and wishes to determine the relative positions of the groups, he may hydrolyze it and ascertain which one of the monocarboxylic acids mentioned above is obtained.

The few examples here cited are sufficient to make clear the principles involved. Whenever one has an *ortho*, *meta* or *para* compound of unknown structure, the position of the substituents can readily be determined by converting the compound into some compound the structure of which is known. Thousands of compounds which may be used as "reference substances" are known. It is sometimes necessary to be cautious lest the reagents used cause a shifting of groups and thus give misleading results.

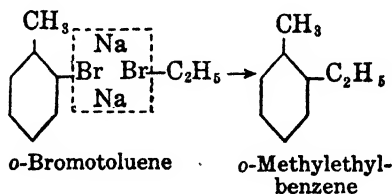
Aluminum chloride, for example, has been found by experience to be an unsafe reagent to use in crucial cases.

Synthesis of Aromatic Hydrocarbons. There are four synthetic methods which are applicable to the preparation of homologs of benzene. *m*-Xylene, for example, can be prepared by heating mesitylenic acid with lime.



Benzene may be prepared by the analogous reaction from *benzoic acid*, C_6H_5COOH . These reactions correspond to the method of preparing methane by heating sodium acetate with soda lime.

The Fittig⁷ synthesis corresponds to the Wurtz synthesis already mentioned. If *o*-bromotoluene and ethyl bromide are together treated with metallic sodium, *o*-methylethylbenzene is formed along with some butane and perhaps other products.



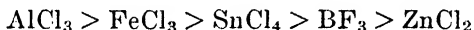
The Fittig synthesis does not generally give good yields of the desired products, but has the distinct advantage that one can rely on the alkyl group taking the position formerly occupied by the halogen, and thus the method can be used when a definite structure is desired.

⁷ R. Fittig (1835-1911), a German, was Professor of Chemistry in Strassburg. This method of synthesis was discovered in 1864, before Kekule's formula had been suggested.

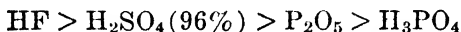
The original **Friedel-Crafts**⁸ synthesis was limited in general to the alkylation of an aromatic nucleus with an alkyl halide using anhydrous aluminum chloride as the catalyst.



This very useful reaction has been extended in scope until at the present time it not only includes the use of aluminum chloride as the catalyst but also several other compounds of lesser activity. Suitable anhydrous halides, listed in the order of decreasing activity, are



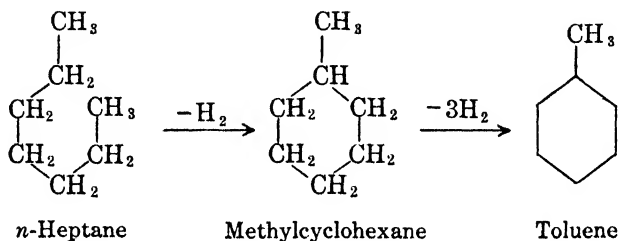
By modifying the conditions of reaction the following catalysts may be used. They are listed in the decreasing order of their importance.



Not only may the catalyst be varied but also the aliphatic reactant. It is of practical significance that both olefins and alcohols can be used in place of the corresponding alkyl halides. Cumene (p. 419) and styrene (p. 420) are produced industrially by the use of the appropriate olefin with a suitable catalyst. Tertiary butylbenzene derivatives (p. 419) are made by using *tert.* butyl alcohol. The Friedel-Crafts method has the disadvantage that one cannot be sure of the arrangement of the groups in the final hydrocarbon, because groups sometimes change their position during the reaction. Examples of how the Friedel-Crafts synthesis can be used to prepare compounds other than hydrocarbons will be cited later.

⁸ C. Friedel (1832-1899) was a French chemist. While Crafts was a student under him in the Sorbonne in Paris in 1877, the reaction which bears their names was discovered. J. M. Crafts (1839-1917), an American chemist, was, until 1900, President of the Massachusetts Institute of Technology

Aromatization. As a result of the increased demand for toluene caused by World War II, a new industrial process for its production was developed which is based on the conversion of *n*-heptane. The process involves a cyclization of the *n*-heptane to methylcyclohexane followed by a dehydrogenation to toluene. The reaction is a high-temperature one catalyzed by oxides of chromium or molybdenum carried on alumina or magnesia.



Although the yields are excellent, a number of other benzene homologs are also formed when the starting material is a mixture of aliphatic hydrocarbons obtained from petroleum.

Oxidation. The homologs of benzene have one important reaction in common due to the stability of the benzene nucleus toward oxidation. It is possible to oxidize the "side chains" of these hydrocarbons by the use of strong oxidizing agents at rather high temperatures, without breaking the benzene ring. The carbon atom or atoms which are attached to the nucleus are firmly held so that the final products of the oxidation are carboxylic acids. If there are two "side chains," one may be oxidized at a time by careful procedure, but eventually a dicarboxylic acid is formed. If three alkyl groups are attached, a tri-carboxylic acid is formed by oxidation. No matter how long the chain of carbon atoms in the alkyl groups, all are broken off except the one attached to the nucleus. Longer side chains are more easily oxidized than shorter ones.

The effect of chlorine and various other reagents on homologs of benzene will be discussed in connection with the behavior of these reagents toward benzene.

PROBLEMS

1. How do the density and boiling point of benzene compare with those of normal hexane, C_6H_{14} ?

2. What is the least number of carbon atoms which could be present in a carboxylic acid derived from benzene?

✓ 3. A trimethylbenzene on careful oxidation yields two monocarboxylic acids. What can be said regarding the structure of the hydrocarbon?

✓ 4. Write the full structural formula for *p*-cymene. What is the structure of the monocarboxylic acid which would be formed by the careful oxidation of this substance?

✓ 5. What halogen compounds could be used in Fittig's synthesis to prepare in one step the following hydrocarbons: (a) *m*-xylene, (b) *p*-cymene, (c) *o*-isobutyltoluene?

6. What will be formed if the monocarboxylic acid formed by the careful oxidation of 1,3,5-trimethylbenzene is heated with lime?

7. Using the symmetrical ring structure, construct all the possible formulas corresponding to $C_6H_2X_3Y$.

8. The Ladenburg prism formula fails to agree with the fact that the *ortho* dicarboxylic acid derived from benzene is the only one which forms an inner anhydride. Apply the "absolute method" (p. 420) to this formula and note the results on this point.

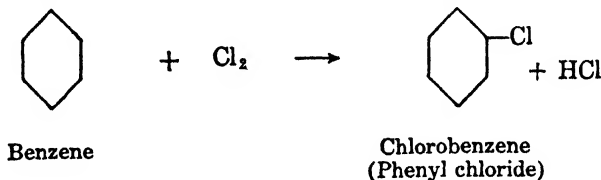
9. The heat of combustion of benzene is 9,977 Cal. per gram. From data previously given (p. 63) determine whether or not benzene is an endothermic or an exothermic compound. It is like the saturated or the unsaturated compounds in this respect? Does its heat of combustion correspond with what you would expect for a triolefin?

10. It is a matter of common observation that a greater proportion of aromatic benzene compounds are solid, as compared with the aliphatic compounds. On what basis can this be explained?

CHAPTER XXIV

HALOGEN SUBSTITUTION PRODUCTS OF BENZENE AND ITS HOMOLOGS

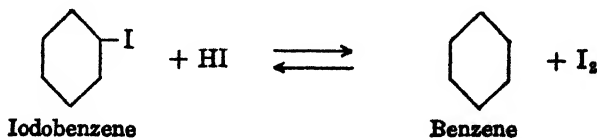
In contrast to the behavior of paraffin hydrocarbons, when benzene is treated with chlorine or bromine in sunlight or other bright light, *addition* of the halogen takes place. However, when benzene is treated with halogens in the dark and in the presence of catalytic agents, substitution takes place and a halogen acid is formed simultaneously with the phenyl halide.



The above reaction is much more easily controlled than the action of chlorine on a paraffin hydrocarbon, and can be stopped with success after one substitution has taken place.

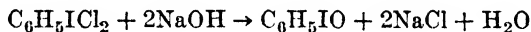
The catalytic agents used to promote substitution in benzene may be iodine, iron, or aluminum as well as some other metals. These catalytic agents are sometimes called "halogen carriers" because they probably first combine with the halogen, and the halogen compound of the metal (probably in an active state) reacts with the hydrocarbon. In the case of iodine, iodine trichloride, ICl₃, is first formed and this is more active chemically than molecular chlorine.

Iodine can be made to substitute for hydrogen in benzene, if a reagent is present which prevents the accumulation of the hydriodic acid which is formed. If hydriodic acid accumulates, the reaction reverses.

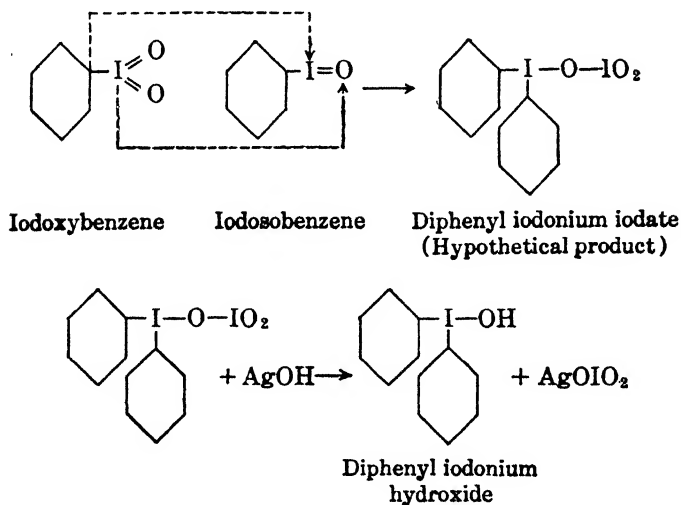


If benzene is treated with iodine in the presence of iodic acid or mercuric oxide, the hydriodic acid is oxidized to iodine and water as fast as it is formed, and *iodobenzene* results. Halogen substitution products of benzene can be made by indirect methods which do not involve the action of the halogen on benzene. These methods will be discussed later.

From phenyl iodide or iodobenzene, **iodonium compounds** can be made by indirect methods. Chlorine acts on iodobenzene to form an addition product which is thought to have the formula $C_6H_5ICl_2$, for by the action of sodium hydroxide it is converted into iodosobenzene, C_6H_5IO .

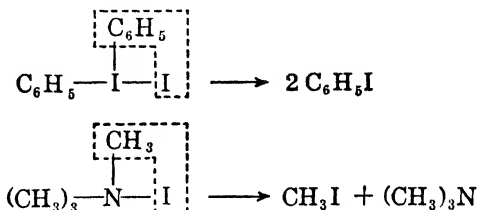


Iodosobenzene is a derivative of iodosic acid, $HOIO$, and can be oxidized to *iodoxybenzene*, $C_6H_5IO_2$, which is an iodic acid derivative. When a mixture of iodosobenzene and iodoxybenzene are treated with moist silver oxide, *diphenyliodonium hydroxide* and silver iodate are formed. Probably the iodosobenzene and iodoxybenzene react to form diphenyliodonium iodate as indicated below, and this reacts with silver hydroxide to give the free base and silver iodate



Diphenyliodonium hydroxide is a strong base like the other substituted "onium" compounds, and is thought to have an analogous structure (p. 192). It forms salts with acids, one of the most interesting of which is *diphenyliodonium iodide*, $(C_6H_5)_2I \cdot I$. This substance

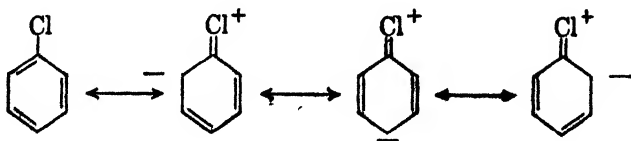
on heating decomposes to give two molecules of iodobenzene, which is analogous to the decomposition of tetramethylammonium iodide into trimethylamine and methyl iodide.



Stability of Phenyl Halides toward Hydrolysis, etc. The simple halogen substitution products of benzene show in one respect a rather strong contrast to the alkyl halides. They do not hydrolyze under ordinary laboratory conditions nor do they react with ammonia, potassium cyanide or with other compounds in the same way as do the alkyl halides. Technically using high pressure and a temperature of 300° , chlorobenzene reacts with sodium hydroxide to yield phenol, $\text{C}_6\text{H}_5\text{OH}$, and sodium chloride. In the Raschig process chlorobenzene is obtained by interaction of HCl , oxygen and benzene over a catalyst at 230° , and the HCl (and phenol) is regenerated by direct catalytic hydrolysis of the chlorobenzene at 425° .

The stability of the halogen substitution products of benzene toward hydrolysis, etc., is not an isolated case, and seems to be correlated with unsaturation which is present in the group attached to the halogen and with the shorter interatomic distance between chlorine and carbon. For example, vinyl chloride, $\text{CH}_2\text{:CHCl}$, is likewise stable toward hydrolysis.

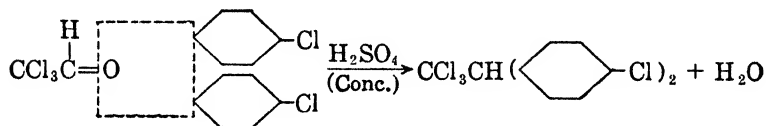
The inert character of the aryl and vinyl halides is attributed to the opportunity for resonance in the halide molecules. This is interpreted as an indication that the linkage assumes the partial character of both a single and a double bond by virtue of resonance between the following structures:



The resonating character of the linkage results in a firmer binding and consequent decrease in reactivity.

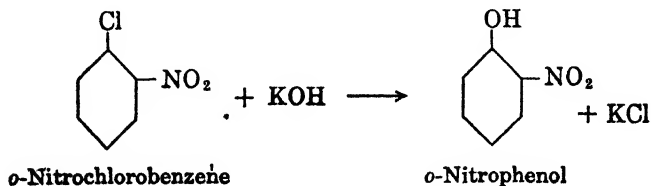
Whether or not this is the true interpretation, it will serve to call attention to the general though perhaps not invariable rule that *whenever an atom or group is attached to the phenyl group, it is held more tightly than when attached to an alkyl group*. This statement does not hold necessarily for attachment to substituted phenyl groups.

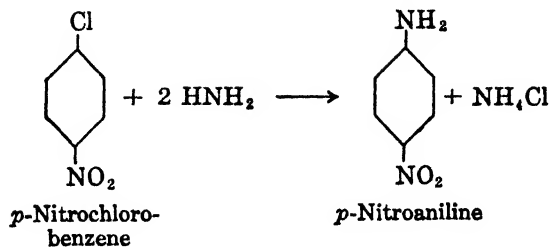
Condensation Reactions. The presence of a halogen on the benzene nucleus activates the *para* hydrogen sufficiently to permit condensation reactions involving this hydrogen. An example of this type of reaction is the preparation of 2,2-bis(*p*-chlorophenyl)-1,1,1-trichloroethane (DDT) by the condensation of chlorobenzene with chloral (trichloroacetaldehyde).



DDT finds wide use as a contact insecticide; 44,000,000 pounds were produced in 1946.

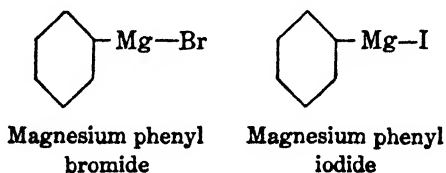
Effect of Other Groups. If in addition to a halogen, there is another group substituted on the nucleus, the halogen may become more easily replaced, depending on the character and position of the other group present. For example, *o*- and *p*-nitro chlorobenzenes, alike, are acted upon either by an alcoholic solution of potassium hydroxide or by an alcoholic solution of ammonia as indicated by the examples.





Alcoholic solutions of the reagents are used because the nitrochlorobenzenes are insoluble in water and do not mix with water solutions. This example indicates how the properties of a group may be modified by the presence of another group. It is interesting to note that a nitro group in the *meta* position does not appreciably affect the reactivity of the halogen compound in this way.

When phenyl halides are treated with metallic magnesium, in the presence of ether, aryl Grignard reagents (aryl = aromatic) are formed similar to those formed from the alkyl halides.

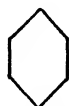


These reagents are more difficult to form and the magnesium is held more tightly by the phenyl group with the result that the reagents are less reactive. Their reactions are in general the same as the alkyl Grignard reagents.

Substitution of More than One Halogen. It is not possible to stop the reaction absolutely with the substitution of one chlorine atom for a hydrogen atom of benzene. When equimolecular proportions of chlorine and benzene are used, some of the di-substitution product is formed and perhaps traces of other derivatives as well. The introduction of further halogen atoms takes place under the same conditions as the first substitution.

We have noted that benzene is symmetrical in structure; all of the hydrogen atoms are similarly situated and a replacement of

any one produces the same result. However, as soon as the first chlorine atom, for example, has replaced one hydrogen the compound loses its symmetry.



Symmetrical
structure



Unsymmetrical
structure

After the chlorine is substituted the remaining hydrogen atoms are not of equal value; they are not replaced with equal ease and three different products may be formed depending on which position the second chlorine attacks. From the standpoint of our previous discussions this unsymmetrical condition is to be expected. A replacement of a hydrogen atom by chlorine would be expected to cause changes in the electron orbits throughout the whole molecule, and to cause hydrogen atoms to be attacked with unequal ease depending on their position with respect to the chlorine atom.

If all hydrogen atoms were replaced with equal ease, one should obtain by chlorination (one step) of chlorobenzene, 40 per cent *o*-dichlorobenzene, 40 per cent *m*-dichlorobenzene and 20 per cent *p*-dichlorobenzene. Experimentally the proportions are quite different; for one set of conditions they were found to be 39 per cent *ortho*, 55 per cent *para* and only 6 per cent *meta*. Evidently the chlorine in chlorobenzene modifies the structures so that substitution in the *para* position is greatly facilitated. It seems likely that this may be due to the existence of the *para* bond postulated by Claus and more recently by Pauling and Lucas.

This directive action which is exemplified above is a very common phenomenon among benzene derivatives as a substituting group is in general directed predominantly to definite positions with respect to the substituent (or substituents) already present. The chlorine atom in chlorobenzene directs any entering group of whatever character predominantly to positions *ortho* or *para* to it. The proportions which are formed are different for

each individual case, and may be modified by change of temperature, catalysts, etc.

If the treatment of benzene with chlorine is continued after the introduction of two chlorine atoms, each atom already present directs further substitution to the positions *ortho* and *para* to it. The result is that, eventually, all of the hydrogen atoms are replaced, and the substance, C_6Cl_6 , is formed. Analogous compounds are formed with other halogens.

p-Dichlorobenzene is used as a fumigant and as a moth repellent. The product of the addition of chlorine to benzene, hexachlorocyclohexane (Gammexane, 666), $C_6H_6Cl_6$, is used as a contact insecticide and one of its geometrical isomers is said to be even more effective than DDT (p. 431).

Action of Chlorine on Toluene. The action which takes place when toluene is treated with chlorine is interesting because there are several possibilities. Toluene may be regarded as methyl benzene, and consequently should have the properties characteristic of benzene. On the other hand it may be regarded as phenyl methane, and as a substituted methane, should show similarities to methane. When chlorine reacts with toluene it may react as it does with benzene, or as it does with methane. In the presence of a chlorine carrier the hydrogen atoms on the ring which are *ortho* or *para* to the methyl group are first replaced. Further treatment causes eventually the replacement of all the hydrogen atoms on the nucleus. In the absence of such carrier, but in the presence of a bright light, especially at the boiling temperature, chlorine replaces one by one the hydrogen atoms of the methyl group. The addition products of toluene and chlorine are not known.

The chlorine substitution products of toluene fall into two classes: (1) those in which the chlorine is attached to the nucleus and (2) those in which the chlorine is in the side chain. The differences between the two types of compounds will be illustrated by a comparison of the properties of the isomers, *p*-chlorotoluene, $ClC_6H_4CH_3$, and benzyl chloride, $C_6H_5CH_2Cl$. The latter is similar to the alkyl halides since it undergoes hydrolysis to form the corresponding alcohol (benzyl alcohol, $C_6H_5CH_2OH$). *p*-Chlorotoluene, like the typical aryl halides, does not undergo

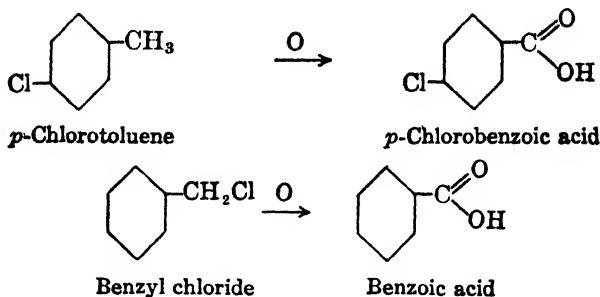
hydrolysis under ordinary laboratory conditions. On oxidation *p*-chlorotoluene yields a chlorine-substituted benzoic acid, while benzyl chloride yields benzoic acid itself.

A Few Halogen Derivatives of Benzene

	Melting Point	Boiling Point
Fluorobenzene, C_6H_5F	-41.9°	84.9°
Chlorobenzene, C_6H_5Cl	< -45°	132°
<i>o</i> -Dichlorobenzene, $C_6H_4Cl_2$	-17.5°	179°
<i>m</i> -Dichlorobenzene, $C_6H_4Cl_2$	-24.8°	172°
<i>p</i> -Dichlorobenzene, $C_6H_4Cl_2$	53°	172-4°
Hexachlorobenzene, C_6Cl_6	229°	326°
Bromobenzene, C_6H_5Br	-31°	157°
<i>o</i> -Dibromobenzene, $C_6H_4Br_2$	1.8°	224°
<i>m</i> -Dibromobenzene, $C_6H_4Br_2$	-6.9°	219°
<i>p</i> -Dibromobenzene, $C_6H_4Br_2$	89°	219°
Hexabromobenzene, C_6Br_6	306°	
Iodobenzene, C_6H_5I	-31.4°	188°
<i>o</i> -Di-iodobenzene, $C_6H_4I_2$	27°	286°
<i>m</i> -Di-iodobenzene, $C_6H_4I_2$	40°	285°
<i>p</i> -Di-iodobenzene, $C_6H_4I_2$	129°	285°
Hexaiodobenzene, C_6I_6	350°	dec.
<i>p</i> -Chlorobromobenzene, C_6H_4ClBr	67°	196°
<i>p</i> -Chloriodobenzene, C_6H_4ClI	57°	228°
<i>p</i> -Bromiodobenzene, C_6H_4BrI	92°	252°

Halogen Derivatives of Homologs of Benzene

	Melting Point	Boiling Point
Benzyl chloride, $C_6H_5CH_2Cl$	-43°	179°
Benzyl bromide, $C_6H_5CH_2Br$	-4°	198°
Benzyl iodide, $C_6H_5CH_2I$	24°	dec.
Benzal chloride, $C_6H_5CHCl_2$	-16°	207°
Benzotrichloride, $C_6H_5CCl_3$	-22°	213-14°
<i>p</i> -Fluorotoluene, $CH_3C_6H_4F$		117°
<i>o</i> -Chlorotoluene, $CH_3C_6H_4Cl$	34°	158-9°
<i>m</i> -Chlorotoluene, $CH_3C_6H_4Cl$	48°	162°
<i>p</i> -Chlorotoluene, $CH_3C_6H_4Cl$	7.4°	163°
<i>o</i> -Bromotoluene, $CH_3C_6H_4Br$	26°	181°
<i>m</i> -Bromotoluene, $CH_3C_6H_4Br$	-40°	183°
<i>p</i> -Bromotoluene, $CH_3C_6H_4Br$	28°	185.2°
<i>o</i> -Iodotoluene, $CH_3C_6H_4I$		211°
<i>m</i> -Iodotoluene, $CH_3C_6H_4I$		204°
<i>p</i> -Iodotoluene, $CH_3C_6H_4I$	35°	211°
Bromo- <i>o</i> -xylene (1, 2, 4), $(CH_3)_2C_6H_3Br$	-2°	214°
Bromo- <i>m</i> -xylene (1, 3, 5), $(CH_3)_2C_6H_3Br$		203°
Bromo- <i>p</i> -xylene (1, 4, 2), $(CH_3)_2C_6H_3Br$	9°	200°



Practically all of the halogen substitution products of aromatic hydrocarbons are insoluble in water but are soluble in alcohol and other organic solvents.

PROBLEMS

1. Treatment of ethyl bromide with alcoholic potassium hydroxide converts it into ethylene. Using the centric formula, picture the equation for the analogous reaction in the case of bromobenzene. A reaction of this type has never been carried out.

2. Write the formulas for 14 aromatic compounds with the formula C_6H_9Br .

3. How do the boiling points of the corresponding chlorine, bromine, and iodine substitution products compare? Does this same relationship hold for the aliphatic substitution products?

4. Would you expect chlorocyclohexane $C_6H_{11}Cl$ to undergo hydrolysis like alkyl chlorides?

5. Work out the formulas for (a) all the trichlorobenzenes, (b) all the pentachlorobenzenes.

6. If chlorobenzene is treated with bromine under conditions which will favor substitution, what compound or compounds would be the first to form?

7. Suppose that a substituted chlorine atom directs 90 per cent of an entering bromine atom to the para position, how much *p*-bromochlorobenzene could be obtained from 10 grams of chlorobenzene?

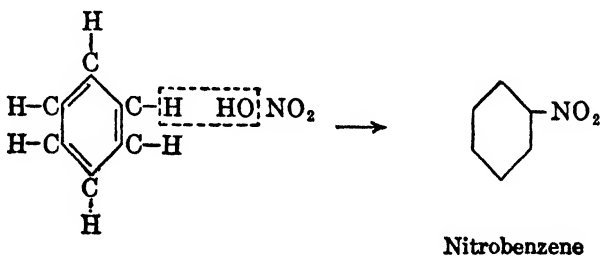
8. Does the fact that the proportion of *o*-dichlorobenzene formed by the chlorination of chlorobenzene is very close to 40% indicate necessarily that in this case chlorine has a negligible effect on chlorination in this position?

CHAPTER XXV

AROMATIC NITRO DERIVATIVES AND SULFONIC ACIDS

Nitro Derivatives

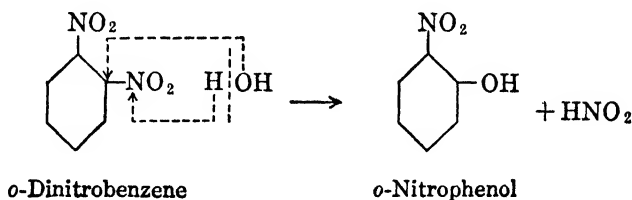
One of the outstanding characteristics of benzene, and the aromatic compounds generally, is their ready reaction with nitric acid. When benzene is treated with fuming nitric acid or with a mixture of ordinary nitric acid and concentrated sulfuric acid, under moderate temperature conditions, a smooth reaction takes place according to the following equation:



Tens of thousands of tons of benzene are treated in this way yearly for the production of **nitrobenzene**. The preparation of nitrobenzene is especially important because it is the first step in a series of reactions which can be carried out for the production of various derivatives of benzene. Nitrobenzene is an oily compound with high boiling point (210.8°) but has an appreciable vapor pressure at the boiling point of water, and so is volatile with steam. Steam distillation is used in its purification.

Nitrobenzene is in most respects unreactive; the nitrogen is firmly held by the carbon of the nucleus and the compound does not hydrolyze or undergo other double decomposition reactions. If, however, there are two nitro groups in *ortho* positions, one of the groups becomes reactive due to the influence of the other, and undergoes hydrolysis and ammonolysis. In this case the

nitro group which breaks off appears to be negative with respect to the carbon to which it is attached, since in reacting it becomes attached to the hydrogen rather than the hydroxyl or amino group.



Ordinarily one would expect a nitro compound to yield nitric acid on hydrolysis rather than nitrous acid.

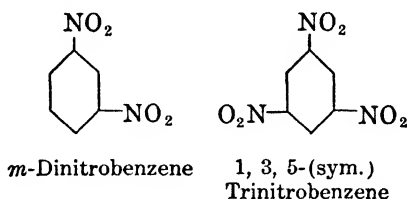
The most important reaction of nitrobenzene is its reduction (p. 214) to the corresponding amine (aniline). This reaction is analogous to the reduction of nitric acid to ammonia, and can be carried out with considerable ease, using a metal to liberate hydrogen from an acid. In the laboratory because of their convenience, tin and hydrochloric acid are most often used, but on a large scale technically, scrap iron and hydrochloric acid are used because of their cheapness.

Continued Nitration. If the temperature during nitration rises above that necessary for the production of nitrobenzene, more highly nitrated products are also formed. Nitrobenzene is not as readily nitrated as benzene itself, however, so nitration can readily be stopped when one nitro group has entered.

The principal substance formed by the continued nitration of nitrobenzene is *m*-dinitrobenzene, though small amounts of the *ortho* and *para* compounds are also formed. It is usually stated therefore that the nitro group directs the second nitro group to the *meta* position. However, the facts are explained just as well by saying that the nitro group has the opposite effect from that of a chlorine atom, that is, it *retards* the formation of substitution products, and the retardation is especially marked in the *ortho* and *para* positions. The fact that nitrobenzene is more difficult to nitrate than benzene itself is in line with the idea that the nitro group has a general retarding influence on further substitution.

It appears therefore that when a nitro group is attached to the benzene nucleus the symmetry is destroyed but in a different manner than is the case when a chlorine atom is attached.

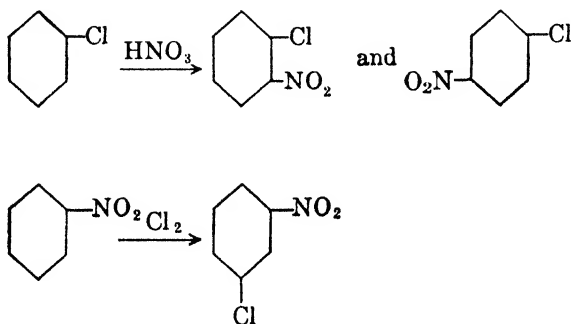
If the treatment is continued longer or at higher temperature, both groups direct the next substitution to the position which is *meta* to both, and symmetrical trinitrobenzene is formed, though with difficulty. The higher nitro compounds have higher melting



points and are more or less explosive, due to the presence of both oxidizing and reducing groups.

Directing of Substituents. The general problem of how groups are directed to particular positions is a very interesting and intricate one. A few facts relating to chlorobenzene and nitrobenzene have already been mentioned.

That the primary influence in directing the substituent to a particular position is due to the substituted group already present is indicated by the fact that the nitration of chlorobenzene yields mostly *o*- and *p*-nitro chlorobenzenes, while the chlorination of nitrobenzene leads to the formation of the *meta* compound principally.



The chlorine atom and the nitro group act in opposite ways, and other groups in general resemble either one or the other, and can be classified as *ortho* and *para* directing or *meta* directing. The *meta* directing groups often appear to retard substitution in all positions, but affect the *ortho* and *para* positions most. The *ortho* and *para* directing groups often increase the ease of substitution, especially in the *ortho* and *para* positions. Some groups, especially OH and NH₂, tremendously increase the ease of substitution.

The more common groups are listed below in the two classes.

**Radicals Directing Principally
to Ortho or Para Positions**

OH(OR)
NH₂(NHR)
Cl, Br, I
CH₃, C₂H₅, etc.

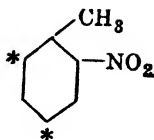
**Radicals Directing Principally
to Meta Positions**

NO₂
COOH, CN
SO₂OH
CHO, COCH₃

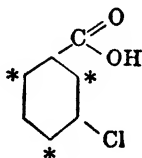
Although many attempts have been made to find a satisfactory basis (other than their directive influence) for grouping these radicals together in this way, a completely adequate basis has never been found. In the groups on the right the atom which is directly attached to the ring is often doubly bonded. That this does not offer a satisfactory basis, however, is shown by the fact that the —CCl₃ group which has no double bond is *meta* directing. (Also according to the best evidence the sulfonic group has co-ordinate valences rather than double bonds.)

Another rule which has more to recommend it is one rather recently suggested and may be formulated as follows. When the atom attached to the benzene nucleus has no other atom attached to it, or is attached to an element which precedes it in the periodic groups, substitution is directed to the *ortho* and *para* positions. If elements in a later periodic group are attached to this atom, the group as a whole becomes *meta* directing.

When there is more than one substituent on a benzene nucleus the two groups may direct a third substituent to the same position (marked with asterisks) in which case there is mutual reinforcement of their influences.



They may, however, tend to direct to different positions in which case different isomers are likely to be formed simultaneously unless one group has a much stronger influence than the other. The *ortho* and *para* directing groups are listed above in the (approximate) order of the strengths of their directing influences. The influence of a hydroxyl group will predominate over that of a halogen, and a halogen will in turn predominate over an alkyl group when their influences are in conflict. The *meta* directing groups do not in general have a strong influence in opposition to the *ortho* and *para* directing class. Thus in *m*-chlorobenzoic acid



the positions *ortho* and *para* to the chlorine are likely to be substituted instead of the position *meta* to the carboxyl group. This fact falls in line with the interpretation that the “*meta* directing” groups in reality possess a retarding effect on the *ortho* and *para* positions rather than a positive tendency to cause substitution in the *meta* position. In either case the “*ortho* and *para* directing” groups generally have a stronger influence.

It is interesting to note that certain groups occupy an intermediate position between that of the *ortho-para* directing groups and the *meta* directing groups. When benzal chloride $\text{C}_6\text{H}_5\text{CHCl}_2$, for example, is nitrated one obtains over 20 per cent *o*-nitrobenzal chloride and about 40 per cent of each of the other isomers.

Another fact in this connection which has both commercial and laboratory applications, is that by change of temperature the distribution particularly between the *ortho* and *para* substitutions can be changed. In some cases it is possible by choice of

conditions to obtain a high yield of either the *ortho* or *para* compound. The electronic structures apparently vary with the temperature. The distribution can also be modified particularly in halogenations, by the choice of catalysts.

The fundamental reasons why certain groups behave in one way while others behave differently, and what determines the type of behavior they will show, are difficult to analyze. That the modification of the electronic structures brought about by the different groups is at the basis of the behavior seems very likely. The question has been studied from this angle especially by Fry—"Electronic Conception of Valence and the Structure of Benzene," Longmans, Green (1921)—and also by Stieglitz, Jour. Amer. Chem. Soc. 44, 1299 (1922). A more modern treatment of this subject is given in Chapter 3 (Fieser) of Gilman's Organic Chemistry (Second Edition).

Nitrotoluenes. The nitration of toluene results in the formation of a mixture of *o*- and *p*-nitrotoluenes. These compounds are made in large quantities and are reduced to the corresponding amino compounds (toluidines) which are important technically. *m*-Nitrotoluene is known, but must be made by an indirect method. Nitration of *o*- or *p*-nitrotoluene results finally in the formation of **trinitrotoluene** (T.N.T.) which is a very important explosive. It is explosive only when it is detonated, and therefore may be handled safely.

Dinitrochlorobenzene is a very important nitro compound which is used in the manufacture of *sulfur black*, one of the most important black dyes. Whereas chlorobenzene cannot readily be hydrolyzed to the corresponding hydroxyl compound, dinitrochlorobenzene can be hydrolyzed, and this is the first step in the utilization of the substance in the manufacture of the dye.

Trinitrochlorobenzene is likewise important technically because it may be hydrolyzed readily to produce the corresponding hydroxyl compound, trinitrophenol or *picric acid*. Both picric acid and ammonium picrate are important explosives and picric acid is used to some extent in dye manufacture.

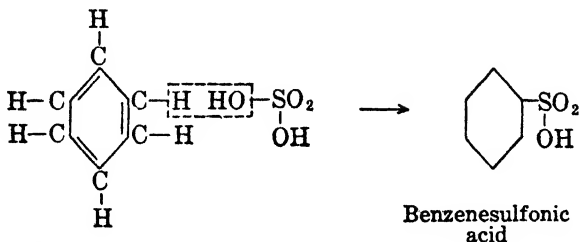
Trinitro tertiary butyl *m*-xylene, in common with other nitro substituted aromatic butyl compounds, has an odor similar to "musk" and is sold for use in perfumery as a substitute for the original article which is obtained from an Asiatic deer.

Nitro Compounds

	Melting Point	Boiling Point
Nitrobenzene, $C_6H_5NO_2$	5.7°	210.8°
<i>o</i> -Dinitrobenzene, $C_6H_4(NO_2)_2$	118°	319° (773 mm.)
<i>m</i> -Dinitrobenzene, $C_6H_4(NO_2)_2$	90°	303° (771 mm.)
<i>p</i> -Dinitrobenzene, $C_6H_4(NO_2)_2$	172°	299° (777 mm.)
1,2,4-Trinitrobenzene, $C_6H_3(NO_2)_3$	61°	
1,3,5-Trinitrobenzene, $C_6H_3(NO_2)_3$	121°	dec.
<i>o</i> -Chloronitrobenzene, $C_6H_4NO_2(Cl)$	32.5°	246°
<i>o</i> -Bromonitrobenzene, $C_6H_4NO_2(Br)$	41.5°	246.4°
<i>o</i> -Iodonitrobenzene, $C_6H_4NO_2(I)$	49°	290°
3,4-Dinitrochlorobenzene, $C_6H_3Cl(NO_2)_2$..	(36.3°, 37°, 38°) ¹	
Trinitrochlorobenzene, $C_6H_2Cl(NO_2)_3$... (Picryl chloride)	83°	dec.
<i>o</i> -Nitrotoluene, $C_6H_4CH_3(NO_2)$	(9.4°, 3.6°) ¹	225.7°
2,4-Dinitrotoluene, $C_6H_3CH_3(NO_2)_2$	70°	300°
3,4-Dinitrotoluene, $C_6H_3CH_3(NO_2)_2$	61°	
3,5-Dinitrotoluene, $C_6H_3CH_3(NO_2)_2$	92.3°	
2,4,6-Trinitrotoluene, $C_6H_2CH_3(NO_2)_3$..	82°	240 exp.
4-Nitro- <i>o</i> -xylene (4) $NO_2C_6H_3(CH_3)_2(1,2)$	29°	258
2,4-Dinitro- <i>m</i> -xylene, $C_6H_3(CH_3)_2(NO_2)_2$	82°	
2,6-Dinitro- <i>m</i> -xylene, $C_6H_3(CH_3)_2(NO_2)_2$	93°	

Sulfonic Acids

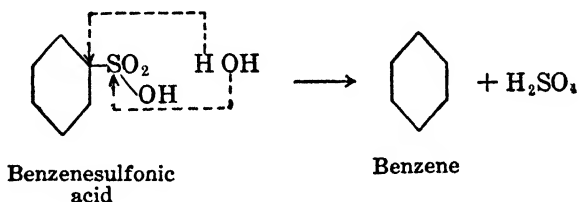
It is characteristic for aromatic hydrocarbons to react under proper conditions with sulfuric acid in a manner similar to that in which they react with nitric acid. The reaction of benzene with sulfuric acid requires a higher temperature and stronger dehydrating conditions than does the reaction with nitric acid so that a mixture of sulfuric acid and nitric acid react to form the nitro compound only. Benzene, when heated with concentrated or fuming sulfuric acid, reacts in the following way.



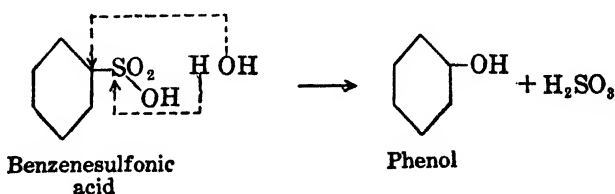
¹ The different melting points listed for the same substance refer to polymorphic forms (p. 513).

This is analogous to the reaction with nitric acid, except that sulfuric acid has two hydroxyl groups and two ionizable hydrogen atoms, and only one is removed by this reaction. The resulting product (sulfonic acid) is therefore an acid with one ionizable hydrogen atom. The phenyl group in replacing the hydroxyl group of sulfuric acid does not greatly alter the strength of the acid so that the sulfonic acids, like sulfuric acid, are strong acids.

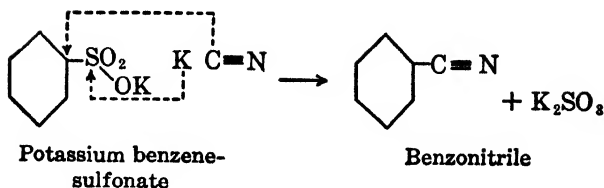
Replacement of the Sulfonic Group. The carbon atom of the benzene nucleus as in other cases holds the attached atom (sulfur) tightly, so it is not easily replaced. However, by heating the sulfonic acids to high temperature with water or with solutions of hydrochloric or sulfuric acid, a hydrolysis takes place forming benzene and sulfuric acid.



By fusing the sulfonic acids with potassium hydroxide (potassium salts of the acids are of course formed as soon as the acids and alkali are mixed), a different reaction takes place which may be regarded as a hydrolysis, but there is a reversal of polarity and a formation of the products indicated.



Both of the end products of this reaction are acidic and are neutralized as formed by the alkali. Exactly a similar reaction takes place when a potassium salt of a sulfonic acid is fused with potassium cyanide.

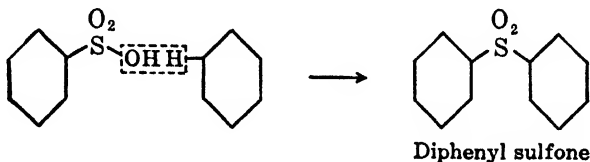


Other Reactions. The sulfonic acids have hydroxyl groups in their structures and in accordance with this fact they react with phosphorus pentachloride to form *sulfonyl chlorides*.



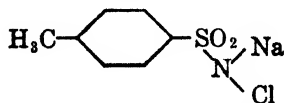
The sulfonyl chlorides react in general like other acid chlorides. They react with ammonia to form *sulfonamides*² and with alcohols to form esters of the sulfonic acids.

Benzenesulfonic acid may react with benzene in the following way.



The product known as *diphenyl sulfone* bears the same relation to sulfuric acid that nitrobenzene does to nitric acid and like nitrobenzene is a neutral substance. It is formed as a secondary product in the sulfonation of benzene.

² An antiseptic which was introduced by Dakin during World War I is sold under the name of "Chlorazene" and is related to and made from a sulfonamide. It is also known as "Chloramine T" and has the structure given below. It is an unusual compound but may be regarded as sodium amide, NaNH_2 , in which both hydrogen atoms are substituted. It is more stable in the presence of water than sodium amide and therefore the chlorosulfonamide has stronger acidic properties than ammonia.



Chlorazene (chloramine T)

Sulfonic Derivatives

	Melting Point	Boiling Point	Solubility Grams in 100 ml.		
			Water	Alcohol	Ether
Benzenesulfonic acid, $\text{C}_6\text{H}_5\text{SO}_3\text{H} \cdot \text{H}_2\text{O}$	65-6°	135-7°	very sol.	very sol.	insol.
Benzene- <i>m</i> -disulfonic acid, $\text{C}_6\text{H}_4(\text{SO}_3\text{H})_2$			very sol.		
Benzene 1,3,5-trisulfonic acid, $\text{C}_6\text{H}_3(\text{SO}_3\text{H})_3$			very sol.		
<i>o</i> -Toluenesulfonic acid, $\text{CH}_3\text{C}_6\text{H}_4\text{SO}_3\text{H} \cdot 2\text{H}_2\text{O}$. .	67.5°	129° (25 mm.)	very sol.	sol.	
<i>m</i> -Toluenesulfonic acid, $\text{CH}_3\text{C}_6\text{H}_4\text{SO}_3\text{H} \cdot \text{H}_2\text{O}$. . .			very sol.	sol.	
<i>p</i> -Toluenesulfonic acid, $\text{CH}_3\text{C}_6\text{H}_4\text{SO}_3\text{H} \cdot 4\text{H}_2\text{O}$. .	107°	146-7° (20 mm.)	very sol.	sol.	
Sulfanilic acid, $\text{NH}_2\text{C}_6\text{H}_4\text{SO}_3\text{H}$	d. 280°		1.1 (20°)	v.s. sol.	v.s. sol.
<i>o</i> -Sulfobenzoic acid, $\text{SO}_3\text{HC}_6\text{H}_4\text{COOH} \cdot (3\text{H}_2\text{O})$	(anhy. 130°)		50	very sol.	insol.
<i>m</i> -Chlorosulfonic acid, $\text{ClC}_6\text{H}_4\text{SO}_3\text{H}$			very sol.		

The sulfonic group is one of the *meta* directing groups and so the introduction of another group, be it a halogen, a nitro group or a second sulfonic group, goes principally to the *meta* position. In the sulfonation of benzenesulfonic acid, the *meta* isomer is the principal product but at the same time there is formed some of the *para* compound. If the *meta* compound is heated for a long time, it is converted into the *para* variety. This behavior is somewhat unusual but is in line with our previous discussion of the effect of temperature on electronic structures.

PROBLEMS

1. Sulfonic acids can be obtained by the oxidation of thioalcohols. What should be produced by the reduction of benzenesulfonic acid?
2. Benzenesulfonic acid can be used in the preparation of ether from alcohol. Write the equations.
3. Compare the formulas of nitrobenzene and "nitroglycerin." What is the structural distinction between a nitro compound and a nitric acid ester?

4. How would you expect the following groups to direct further substitution (1)-COOC₂H₅, (2)-N(CH₃)₂, (3)-CCl₂CCl₃?

5. What isomers would predominate from the introduction of (a) one nitro group into toluene; (b) a chlorine atom into phenyl hydroxide; (c) a bromine atom into benzene-sulfonic acid; (d) a sulfonic group into benzoic acid, C₆H₅COOH; (e) a bromine atom into aniline (phenylamine); (f) a nitro group into benzaldehyde, C₆H₅CHO?

6. Write electronic formulas for nitrobenzene and benzenesulfonic acid.

7. Which would have the higher percentage of sulfur, a normal solution of sulfuric acid or a normal solution of benzenesulfonic acid?

8. If nitrobenzene were heated with fused alkali, it might break up as the sulfonic acids do. Would there be any experimental difficulty in carrying out this procedure in the laboratory, which would not be present in the case of the sulfonic acid?

CHAPTER XXVI

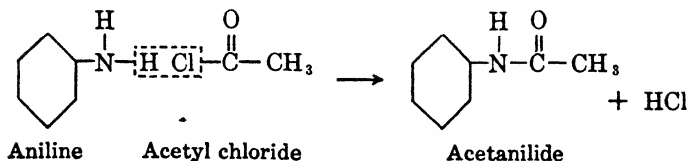
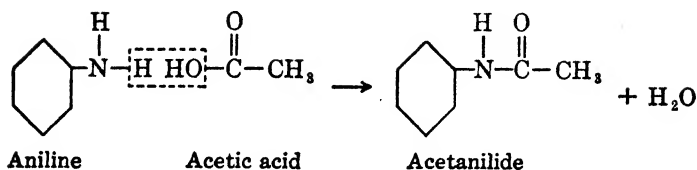
AROMATIC AMINO DERIVATIVES

Aniline (ǎn'ī-līn), $C_6H_5NH_2$, as has already been stated, is formed by the reduction of nitrobenzene in acid solution. When prepared by reduction with tin and hydrochloric acid, the aniline hydrochloride produced forms double salts with stannous and stannic chlorides, $C_6H_5NH_3Cl \cdot SnCl_2$ and $(C_6H_5NH_3Cl)_2 \cdot SnCl_4$, which crystallize from the solution. They are decomposed by treatment with alkali, which precipitates the hydroxides of tin and leave the aniline uncombined. $C_6H_5NH_3OH$ is formed but is even more unstable than ammonium hydroxide and so breaks down into free aniline and water. When conditions other than those mentioned are used in the reduction of nitrobenzene, other compounds which lie between nitrobenzene and aniline in their degree of reduction are formed. These will be discussed later.

The usual industrial preparation of aniline is by the reduction of nitrobenzene with iron and 30 per cent hydrochloric acid. It is also made by treating chlorobenzene with ammonia under pressure and at a high temperature.

Similarity of Aniline to the Aliphatic Amines. In many respects aniline is like the aliphatic amines and hence like ammonia itself. It forms salts with hydrochloric acid, sulfuric acid, etc., and these salts like the salts of all weak bases are relatively unstable in water solution and, due to hydrolysis, give a strong acid reaction. The phenyl group makes aniline weaker in base-forming property than ammonia. This is in accordance with the general fact that unsaturation increases acidity, and hence decreases the base-forming property. In addition to forming double salts with the chlorides of tin, aniline also forms double salts with platinum chloride, $PtCl_4$, and other salts, and in this respect also resembles other amines.

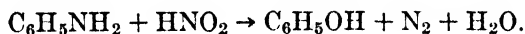
When aniline is boiled with glacial acetic acid or treated with acetic anhydride or acetyl chloride, **acetanilide**, $C_6H_5NHCOCH_3$, is formed, and the reaction is analogous to the formation of acetamide from ammonia.



Acetanilide is therefore a substituted amide. It is used in medicine, and is a frequent ingredient of proprietary headache and cold tablets. It has the advantage of being very cheap, since both the acetic acid and aniline out of which it is made are relatively inexpensive and the reaction is an easy one to carry out.

When aniline is heated with alkyl halides reactions take place which correspond to those of the aliphatic amines; addition takes place forming salts of secondary amines (p. 189). These dissociate and may add on alkyl halides again, etc., so that eventually tertiary amines and finally quaternary ammonium compounds are formed.

Nitrous acid acts on aniline at room temperature or above, in the same way that it acts on aliphatic primary amines. Nitrogen gas, phenyl hydroxide (phenol), and water are formed.

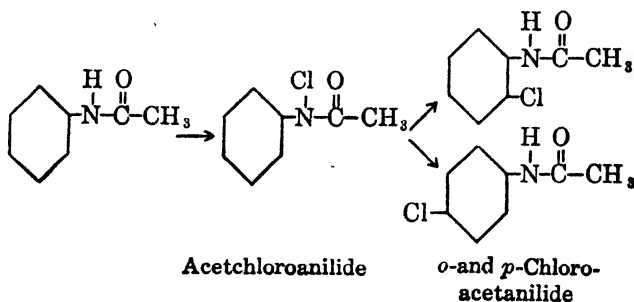


In aniline, however, the nitrogen is more tightly held by the carbon atom than in the case of the alkyl amines. As a result, if the solution is kept cool, the nitrogen remains attached to the nucleus and the important *diazo compounds* (to be discussed in Chapter XXVII) are formed. This constitutes one of the several points of contrast between aniline and the aliphatic amines. The discussion of other dissimilar reactions follows.

Reactions with Halogens. When treated with bromine, for example, aniline very readily yields symmetrical tribromoani-

line. It is only necessary to use a solution of bromine (bromine water) to bring about this reaction practically instantaneously.¹ The contrast between this behavior and that of benzene which must be treated with liquid bromine in the presence of a catalyst to produce the monosubstitution product, is very marked. The presence of the amino group greatly facilitates the introduction of other substituents. In this respect aniline very much resembles phenol, C_6H_5OH , which also yields halogen and other derivatives very easily. Of all of the simple derivatives of benzene these two classes of compounds are most reactive. In many cases reagents which have no effect on benzene react with these amino and hydroxyl compounds readily, and by this means many different groups may be substituted on the benzene nucleus.

As the treatment of aniline with chlorine or bromine produces tri-halogen substitution products with great ease, the mono-substituted anilines must be made in some other way. By conversion of aniline into acetanilide the ease of substitution is much decreased so that it is possible to form mono-substitution products. When chlorine acts on acetanilide it first substitutes for hydrogen attached to the nitrogen, and at higher temperature it changes places with a hydrogen atom on the nucleus.

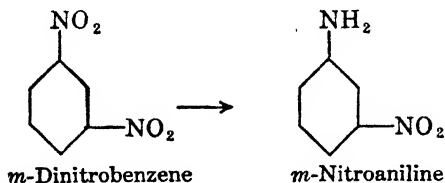


¹ The ease of the action of bromine on aniline, and the insolubility of the tribromoaniline were the basis for an early method of extracting bromine from sea water. The sea water was treated with chlorine which liberated bromine from the bromides present. The bromine then reacted with aniline to form the insoluble tribromoaniline, from which the bromine was recovered. About 1800 gallons of sea water yield one pound of bromine. The demand for bromine has been increased greatly in connection with the use of tetraethyllead (p. 44).

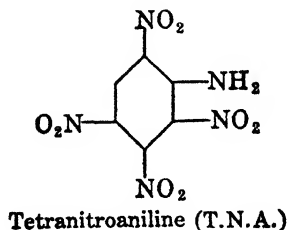
Chlorine attached to nitrogen does not constitute a stable combination, but chlorine attached to carbon does, therefore when this latter combination is formed it does not revert. The chlorine substituted acetanilides can be hydrolyzed to form the chloroanilines and acetic acid. In this respect they behave like other amides.

Nitration. Aniline is also much more easily nitrated than other types of derivatives of benzene, so that if treated directly with a mixture of sulfuric and nitric acids, three nitro groups are likely to be introduced and at the same time the aniline is oxidized to some extent. *p*-Nitroaniline, $C_6H_4(NH_2)NO_2$, an important substance used in the manufacture of dyes (a dye intermediate), cannot, therefore, be made practically by the direct nitration of aniline. Aniline is first converted into acetanilide, which can be nitrated to produce a high yield of *p*-nitroacetanilide. This substance like other amides can be hydrolyzed, and the nitroaniline thus recovered.

o-Nitroaniline can be made in a similar manner except that the conditions of nitration are changed so as to give more of the *ortho*-compound. *m*-Nitroaniline can be made by a partial reduction of *m*-dinitrobenzene which itself is made by nitrating benzene.

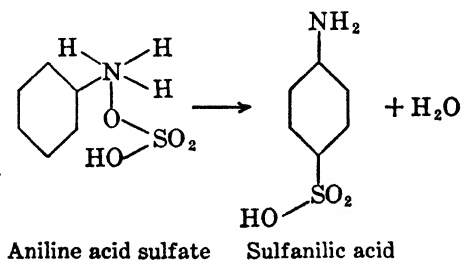


When *m*-nitroaniline is nitrated with a mixture of sulfuric and nitric acids, *tetranitroaniline* is formed. It is an explosive known as T.N.A.

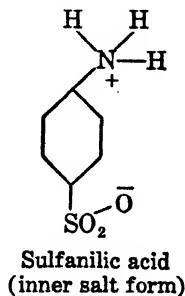


The nitroanilines are more weakly base forming than aniline itself, because the nitro groups increase acid properties and decrease basic properties of neighboring groups. In trinitroaniline the base-forming property of the amino group has practically vanished.

Sulfanilic acid is prepared in the laboratory by treating aniline with concentrated or even fuming sulfuric acid, and commercially is made by heating aniline acid sulfate to about 200° for several hours.



Although the formula of sulfanilic acid is usually written as above, its structure is not that of an amine since it does not form salts with acids. As would be expected of a substance with an amino as well as an acid group, it forms an internal salt which has the following formula:

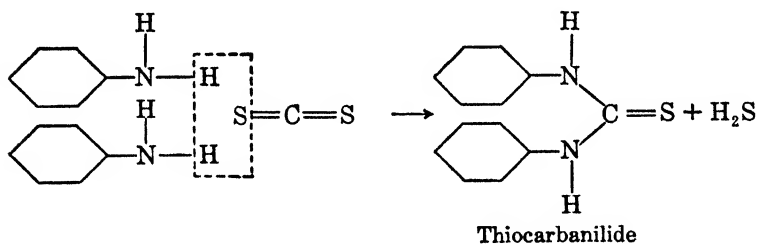


When sulfanilic acid is treated with bromine, symmetrical tri-bromoaniline is formed by the replacement of the sulfonic group and two hydrogen atoms by bromine. The replacement of a sulfonic group by a halogen is rather a general reaction. When

sulfanilic acid is fused with sodium hydroxide it breaks in such a way as to give aniline and sodium sulfate.

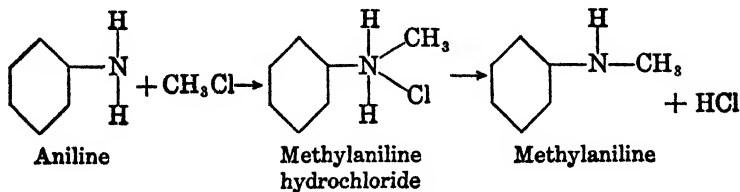
Sulfanilamide, the amide of sulfanilic acid, has come into great prominence in the medical field in recent years. As a compound it has been recognized for several decades, but the recent discovery of its therapeutic value in numerous infections is regarded as one of the outstanding medical discoveries of this century. *Sulfapyridine* (p. 584) is even more valuable for some purposes and *sulfathiazole* (p. 602) is also valuable. The use of the latter compounds, as well as others, has been an outgrowth of the use of sulfanilamide.

When aniline is heated with carbon disulfide in the presence of a little sulfur which acts as a catalyst, **thiocarbanilide** is formed.



It is used as an accelerator in rubber vulcanizing (p. 393), and in the manufacture of dyes. It crystallizes readily in leaflets which melt at 151° .

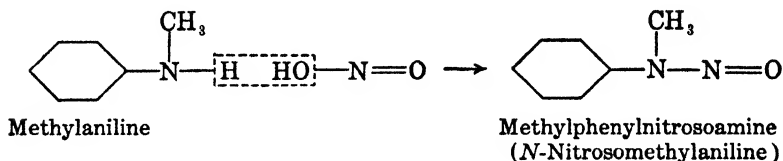
The most important aromatic secondary and tertiary amines are those which have in their structures alkyl groups in addition to the phenyl group, such as **methylaniline**, $\text{C}_6\text{H}_5\text{NHCH}_3$, and **dimethylaniline**, $\text{C}_6\text{H}_5\text{N}(\text{CH}_3)_2$. These substances along with the quaternary compounds can be made by the action of aniline on methyl chloride, bromide or iodide.



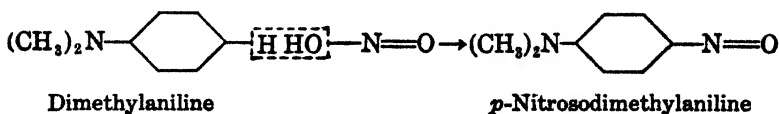
The alkyl iodides, as usual, are the most reactive. Methyl iodide is the only one of the methyl halides which forms a quaternary compound at all readily.

Technically, **dimethylaniline** is the more important of the two, and it is made by heating methyl alcohol and aniline sulfate to about 200°. Under these conditions, the methyl alcohol probably reacts first to form methyl acid sulfate, which then reacts with the aniline in a way analogous to that pictured for methyl chloride. The dimethylaniline is separated from the unchanged aniline and from the methylaniline by taking advantage of the fact that only primary and secondary amines are capable of reacting with acetyl chloride (ammonolysis, p. 156). By treating the mixture with acetyl chloride the acyl derivatives of aniline (acetanilide) and monomethylaniline are formed and are so slightly volatile that the dimethylaniline can be removed by distillation.

Methylaniline like aliphatic secondary amines reacts with nitrous acid to form a nitrosoamine.

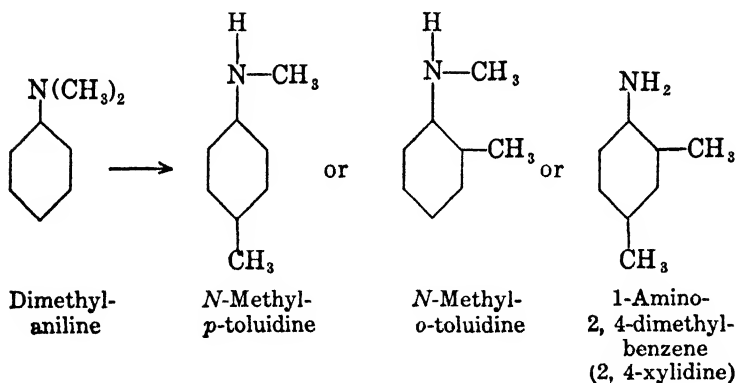


Dimethylaniline, which is a tertiary amine, does not behave like the aliphatic tertiary amines, since it reacts with nitrous acid. We have already noted that the hydrogen atoms of the nucleus in aniline are much more easily substituted than in benzene itself. The presence of the amino group makes substitution so much more easy that in this case nitrous acid is able to bring about a substitution reaction, after the following scheme.



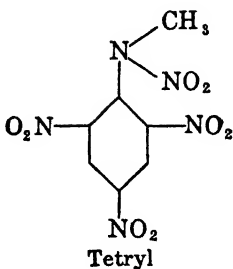
This substance (or rather its hydrochloride, for it is a basic substance) is formed when dimethylaniline in hydrochloric acid solution is treated with the calculated amount of sodium nitrite. The *p*-nitrosodimethylaniline hydrochloride is decomposed with sodium carbonate and the free *p*-nitrosodimethylaniline is recovered by extraction with ether. This substance is of some importance as a dye intermediate.

Another reaction indicates the ease with which substitution may take place in the anilines. When dimethylaniline is heated to a high temperature (about 300°), it undergoes a molecular rearrangement whereby the methyl groups attached to the nitrogen trade places with the *ortho* or *para* hydrogen atoms of the ring as indicated.

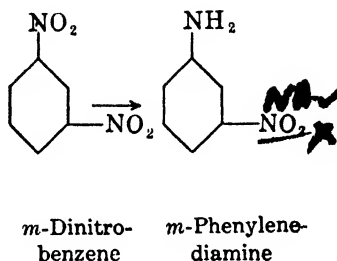
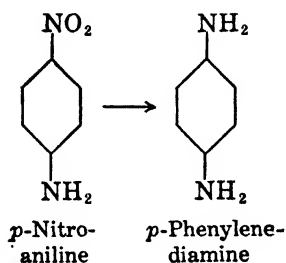


This is an unusual change because it means that a carbon-nitrogen linkage is broken ; however, it requires a high temperature to bring about the reaction and it is not reversible. It is used as a technical method for making 2,4-xylydine. The monomethylaniline undergoes the same reaction.

When heated with a mixture of nitric and sulfuric acids, dimethylaniline is nitrated and at the same time one of the methyl groups is removed by oxidation and replaced by a nitro group, as shown below. This is the explosive which is known as *tetryl*.

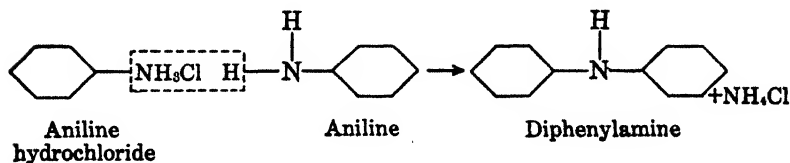


When either dinitro compounds or nitroanilines are reduced, the corresponding diamines are produced. Thus *p*-nitroaniline and *m*-dinitrobenzene give the following:



These are called *phenylenediamines* (C_6H_4 = *phenylene*). All three phenylenediamines are used in the preparation of dye-stuffs. They are similar in properties to the anilines, and as a rule are able to undergo, twice over, the reactions characteristic of aniline.

Diphenylamine and **triphenylamine** are amines which contain only aryl and no alkyl groups. When a mixture of aniline and aniline hydrochloride is heated above 200° , diphenylamine is formed.



This substance is used in the manufacture of dyes and as a stabilizer for explosives. When mixed with the latter safety in handling and transportation is increased.

The presence of the two phenyl groups has the effect of making the substance very weak in base-forming properties. It does form salts with strong concentrated acids but these salts are largely hydrolyzed in the presence of water. The weak acidic property of ammonia is, however, appreciably increased by the substitution of two phenyl groups for two of the hydrogen atoms, so that diphenylamine has weak acid properties and forms metallic derivatives which are comparatively stable, but, of course, are hydrolyzed in the presence of water.

Triphenylamine, $(C_6H_5)_3N$, may be formed by treating the potassium derivative of diphenylamine with bromobenzene at high temperature. Its base-forming properties are entirely negligible, due to the presence of the three phenyl groups.

Benzyl amine, $C_6H_5CH_2NH_2$, is a type of amine which shows considerable contrast to the aromatic amines which we have considered. It is closely related to the aliphatic amines as it can be made by heating benzyl chloride, $C_6H_5CH_2Cl$, with ammonia, and also by treatment of the appropriate amide with bromine and alkali. It is much stronger in basic properties than aniline. The contrast shown is due to the fact that the amino group is not directly attached to the nucleus.

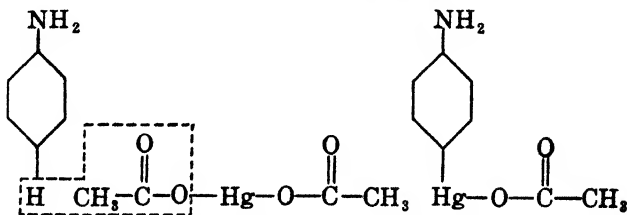
Toluidines. The three possible amino toluenes (*toluidines*), $CH_3C_6H_4NH_2$, may be prepared from the corresponding nitro-toluenes. The *ortho* and *para* compounds are of considerable importance in dye manufacture. They are similar to aniline in properties. The *xyloidines* or amino xylenes, $(CH_3)_2C_6H_3NH_2$, also have properties similar to aniline.

When mercuric acetate is allowed to react with aniline it readily forms substitution products. This illustrates the ease of substitution in aniline, and at the same time serves to call attention to a large number of mercury derivatives of organic compounds² that are known.

² See F. C. Whitmore. "Organic Compounds of Mercury," Chem. Catalog Co.

Amino Compounds

	Melting Point	Boiling Point
Aniline, $C_6H_5NH_2$	-6°	184°
<i>o</i> -Phenylenediamine, $C_6H_4(NH_2)_2$	102.3°	256.8°
<i>m</i> -Phenylenediamine, $C_6H_4(NH_2)_2$	63°	283.4°
<i>p</i> -Phenylenediamine, $C_6H_4(NH_2)_2$	140°	267°
<i>o</i> -Toluidine, $CH_3C_6H_4NH_2$	$-21^\circ, -15.5^\circ$	199.7°
<i>m</i> -Toluidine, $CH_3C_6H_4NH_2$	-31.5°	203°
<i>p</i> -Toluidine, $CH_3C_6H_4NH_2$	45°	200.3°
<i>v-o</i> -Xylidine, (1,2), (3), $(CH_3)_2C_6H_3NH_2$	$<-15^\circ$	225°
unsym.- <i>o</i> -Xylidine (1,2), (4), $(CH_3)_2C_6H_3NH_2$	49°	226°
<i>v-m</i> -Xylidine (1,3), (2), $(CH_3)_2C_6H_3NH_2$		216°
unsym.- <i>m</i> -Xylidine (1,3), (4), $(CH_3)_2C_6H_3NH_2$		212°
sym.- <i>m</i> -Xylidine (1,3), (5), $(CH_3)_2C_6H_3NH_2$		220°
<i>p</i> -Xylidine (1,4), (2), $(CH_3)_2C_6H_3NH_2$	15°	217°
sym. Pseudocumidine (5), $NH_2C_6H_2(CH_3)_3$ (1,2,4)		235°
Mesidine (2), $NH_2C_6H_2(CH_3)_3$ (1,3,5)	$<-15^\circ$	230°
Isoduridine (4), $NH_2C_6H_2(CH_3)_3$ (1,2,3,5)	23°	255°
Pentamethylaminobenzene, $NH_2C_6(CH_3)_5$	151°	277°
Monomethylaniline, $C_6H_5NHCH_3$	-57°	198.8°
Ethylaniline, $C_6H_5NHCH_2CH_3$	-63.5°	206°
Dimethylaniline, $C_6H_5N(CH_3)_2$	2.5°	193°
Diethylaniline, $C_6H_5N(CH_2CH_3)_2$	-38.8°	213.5°
Methylenediphenyldiamine, $CH_2(NHC_6H_5)_2$	65°	
Ethylenediphenyldiamine, $C_2H_4(NHC_6H_5)_2$	65°	
Ethylenemonophenyldiamine, NH_2CH_2- $CH_2NHC_6H_5$		263°
Ethyleneiso-		
butylidene-		
diphenyldia-		
mine, $CH_2N(C_6H_5)$ $\begin{array}{l} \diagup \\ \diagdown \end{array} \begin{array}{l} CH_2N(C_6H_5) \\ CH_2N(C_6H_5) \end{array}$	95°	
Diphenylamine, $C_6H_5NHC_6H_5$	52.8°	302°
Triphenylamine, $(C_6H_5)_3N$	127°	365°
Thionylaniline, $C_6H_5N:SO$		200°
		184°
Thionyl- <i>o</i> -toluidine, $CH_3C_6H_4N:SO$		(100 mm.)
Thionyl- <i>m</i> -toluidine, $CH_3C_6H_4N:SO$		220°
Thionyl- <i>p</i> -toluidine, $CH_3C_6H_4N:SO$	7°	224°



Anilinemercuric acetate

p-Aminophenylmercuric acetate

The method just mentioned is the most fruitful method of obtaining mercury derivatives of aromatic compounds, of which a large number have been made, partly with the purpose in view of obtaining valuable compounds for the treatment of disease.

In some cases it has been found advantageous to substitute mercury on the nucleus in order later to substitute a halogen in the same position. Treatment of a mercury derivative such as the above, with a halogen easily breaks the carbon-mercury bond. Thus *o*-iodophenol which is difficult to prepare by other means can be prepared by treating phenol with mercuric acetate and then treating the product with iodine.

PROBLEMS

1. Which of the amines discussed in the text would react with acetic anhydride?

2. Write the structural formula for diphenyl-*N*-nitrosoamine. How could it be made?

3. How much tin would be necessary to reduce 8 g. of nitrobenzene, if the tin were converted to stannous chloride?

4. Write the formula for formanilide (analogous to acetanilide).

5. Work out all the possible structures for aminoxylenes or xyli-dines. All have been prepared.

6. Write the formula of the amide which would be used for the preparation of benzyl amine.

7. How could *o*-phenylenediamine be prepared? How much nitrogen gas measured at standard conditions would be produced by the action of nitrous acid on 0.1 gram of this substance?

8. Write the formulas and give the names for the compounds formed when monomethylaniline undergoes molecular rearrangement at high temperature.

9. What are the outstanding differences between aniline acetate and acetanilide? Are their water solutions neutral, acid or alkaline?

10. Which would have the stronger basic properties, *N*-nitrosomethylaniline or *p*-nitrosomethylaniline?

11. Why, in the formation of T. N. A. does nitration stop while one position in the ring is still unsubstituted?

12. Ethylmethoxyphenylamine oxide is optically active. Is this in line with the idea of coordinate valence?

CHAPTER XXVII

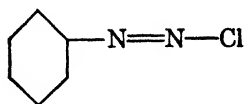
DIAZO AND RELATED COMPOUNDS

Perhaps the formation of diazo compounds¹ is the most distinguishing feature of aromatic compounds as contrasted with aliphatic compounds. The primary amines in which the amino group is attached to the carbon of the nucleus, react with nitrous acid, when kept cold, to form these typical compounds in which nitrogen remains attached to the nucleus. When warmed in water solution these compounds break up to give nitrogen gas, a phenol and water. The end result when the reaction is carried out at moderate temperatures is therefore exactly analogous to the primary aliphatic amines. The term "diazo" (dī-ăz'-ô) is used because of the two nitrogen atoms present (French, *azote*-nitrogen) which, when the solution is warmed, pass off as nitrogen gas, N_2 . The formation of the diazo compounds illustrates again the firmness with which atoms are held by the carbon of the benzene nucleus. In aliphatic compounds nitrogen gas is ordinarily evolved even at low temperature.

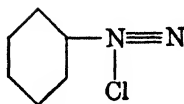
Structure. When aniline in strongly acid solution is treated with sodium nitrite solution (this is the most common way of treating with nitrous acid), there is formed a substance which has the molecular formula $C_6H_5N_2Cl$. Since the substance is obtained from aniline, it obviously would be expected to have a phenyl group attached to a nitrogen atom as in aniline. Necessarily the other nitrogen atom must be attached to the first nitrogen atom and the chlorine atom must be attached to one or the other of the two nitrogen atoms, since there is no other possible position. The formulas advanced by Kekule and Blomstrand² respectively are:

¹ These were discovered by Peter Griess (1829-1888) who at the time was working with Hofmann (p. 185) in England. During his later years he was chemist for a large brewery in Burton-on-Trent, England.

² C. W. Blomstrand (1826-1897) was a Swedish chemist, professor in the University of Lund. His work was to a large extent in the field of inorganic chemistry.



I (Kekule)



II (Blomstrand)

In order to have a basis upon which to decide between these two formulas, it is necessary to consider the properties of the compound actually obtained, which has all the characteristics of a salt. It is a conductor of electricity, gives evidence of ionization and one of the ions formed is the chloride ion. It is, as a matter of fact, a neutral salt and this means that since it is a salt of hydrochloric acid, a strong acid, it must be the salt of a strong base, otherwise it would give an acid reaction.

The first formula might be considered as derived from nitrous acid by the substitution of the $C_6H_5N:$ group for the oxygen, and chlorine atom for the hydroxyl group. The $C_6H_5N:$ group in place of the oxygen would not be expected fundamentally to alter the character of the nitrous acid as this group does not differ greatly from oxygen in its acid or base forming tendencies. The chlorine atom in the place of the hydroxyl of the weak acid would make the substance of the nature of an acid chloride, and not a salt, much less the salt of a strong base. On this basis formula I cannot be said to fit the substance.

Formula II, on the other hand, represents (in terms of the older method of formulation) a derivative of ammonium chloride in which one of the hydrogen atoms is replaced by the phenyl group and the other three hydrogen atoms are replaced by the trivalent nitrogen atom. It would be then a type of quaternary ammonium salt. It is a remarkable fact already noted (p. 192) that all of the quaternary ammonium salts are salts of strong bases no matter what groups are substituted for the hydrogen atoms. This fact argues very strongly for formula II as representing the salt which is formed under the conditions described except that in accordance with our previous discussions (p. 188) the chlorine which is always an ion should not be connected with the nitrogen by a bond. In accordance with this structure the substance is called **benzenediazonium chloride** (*phenyl diazon-*

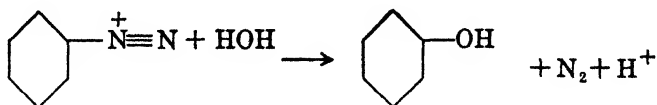
ium chloride) to show its relationship to the other "onium" compounds.

If aniline in the presence of strong acids other than hydrochloric acid is treated with a nitrite, similar reactions take place with the formation of benzenediazonium sulfate or nitrate, etc. Such reactions as these are called *diazotizations*. As a usual laboratory procedure the salt itself is not isolated in pure form, but is used in solution, for the preparation of some other compound. The salts can be isolated in pure form and are generally explosive. This is especially true of the nitrate.

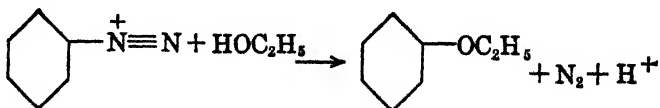
Reactions in Which Nitrogen Gas Is Evolved. The reactions of the diazonium salts may be divided for convenience into two classes: (1) those in which nitrogen gas is evolved, and (2) those in which the nitrogen remains in combination. The most important reactions of the first type are those listed below.

The course which these reactions pursue is not well understood. Since the reactions take place in the same way (in general) whether the diazonium salt is a chloride, bromide, nitrate, sulfate, etc., we may indicate the reactions as those of the diazonium ion. The crucial result in each case is the liberation of nitrogen gas (electrically neutral) and the assembling of what remains into stable structures. Just why the particular products are the principal ones formed in each case cannot be answered with certainty.

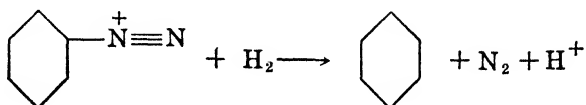
(1) Decomposition of the diazonium salt by the action of warm water; **replacement of the diazonium group by a hydroxyl group.**



(2) Decomposition in the presence of a hot alcohol; **replacement of the diazonium group by a methoxy or ethoxy group.**

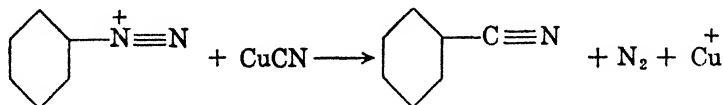


(3) Decomposition in the presence of hot alcohol; **replacement of diazonium group by hydrogen**. Simultaneously with reaction (2) the alcohol may act as a reducing agent and furnish hydrogen to reduce the phenyl group to benzene, the alcohol itself being oxidized to aldehyde.



Reaction (3) predominates in case of a diazonium salt derived from a nitroaniline or sulfanilic acid but the simple benzenediazonium salt itself decomposes principally according to equation (2) in the presence of alcohol.

(4) **Replacement of the diazonium group by halogens or the cyanide group**. When benzenediazonium chloride is decomposed with water there is formed a small amount of chlorobenzene in addition to the phenol. This happens especially when the solution is very strongly acid with hydrochloric acid. When cuprous chloride is present in addition to hydrochloric acid, the reaction goes principally to form chlorobenzene, and constitutes a method of preparation of chlorobenzenes. Likewise benzenediazonium bromide in the presence of hydrobromic acid, and cuprous bromide, gives bromobenzene. Benzenediazonium iodide, when decomposed in the presence of hydriodic acid or other iodide alone, gives a good yield of iodobenzene, and this is generally the most convenient method of preparing this type of compound. Benzenediazonium chloride when decomposed in the presence of cuprous cyanide and potassium cyanide produces benzonitrile.



The cuprous salts in these cases act as catalytic agents through the formation of intermediate products.

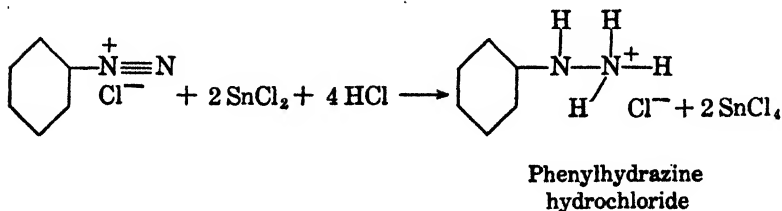
There are other groups that can also be introduced by proper treatment of the diazonium compounds, but the reactions are not

of so much importance. The use of cuprous salts was introduced by Sandmeyer³ and these are called Sandmeyer reactions. Copper powder in the presence of the appropriate halogen acid may be used instead of solutions of cuprous salts (Gattermann's⁴ diazo reaction).

By use of reactions of the first type in which nitrogen is replaced, the diazonium salts may be used to prepare phenols, ethers, hydrocarbons, halogen substitution products and the nitriles. The nitriles can easily be converted to acids, and their derivatives, and so the diazonium salts have been very valuable in synthetic work. They have the advantage that they need not be isolated but may be used immediately after they are formed in solution. The amino compounds which are generally relatively easy to obtain are treated in acid solution with the necessary amount of sodium nitrite, while the solution is kept cool. After the diazotization which requires only a few minutes, the succeeding steps may be carried out so that the whole process starting with the amino compound does not involve much more time than the average single operation.

Reactions in Which Nitrogen Remains in Combination. The most important reactions in which nitrogen remains attached to the benzene nucleus are the following:

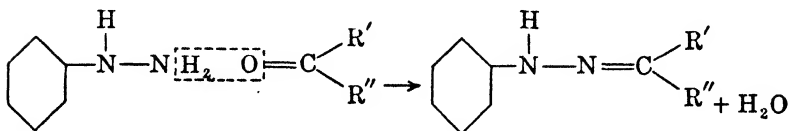
(1) **Reduction.** Benzenediazonium chloride for example can be reduced in acid solution by the use of stannous chloride according to the equation,



³ T. Sandmeyer (1854-1921) devoted himself primarily to the work of a technical dye chemist and was the discoverer of many new dyes. He was a Swiss.

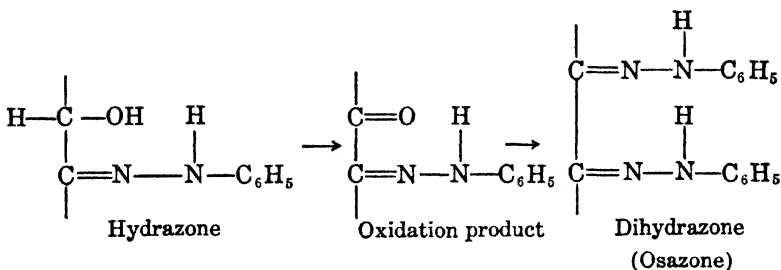
⁴ Ludwig Gattermann (1860-1920), was Professor of Chemistry at Freiburg, Germany.

Phenylhydrazine which is formed by this reaction was the first of the hydrazines to be discovered and is the most important of the compounds of this type. It reacts, as we have already noted with ketones and aldehydes, in the following manner:



to produce hydrazones. *Hydrazides* correspond to *N*-substituted amides $\text{R}-\text{CONHNHR}$ and are formed by interaction between a hydrazine and an acid chloride or ester.

With hydroxy aldehydes and hydroxy ketones (sugars) it acts first in the manner indicated above, then an excess of phenylhydrazine, if present, oxidizes the resulting hydrazone to a ketone (or aldehyde). More phenylhydrazine then reacts with this carbonyl compound in the usual way to form a dihydrazone or osazone (p. 342). In the formation of the dihydrazones three molecules of phenylhydrazine are required for each sugar molecule. The phenylhydrazine which acts as an oxidizing agent in the second step is reduced to aniline and ammonia.

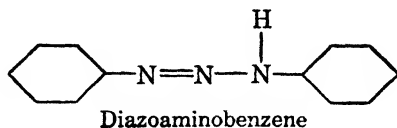


The dihydrazones are frequently crystalline and serve as means of identifying sugars. They can be reconverted into sugars as previously indicated.

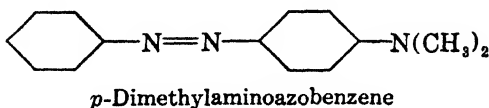
Phenylhydrazine is a basic substance as would be expected from its formula, and it forms salts, the most common of which is the hydrochloride, $\text{C}_6\text{H}_5\text{NHNH}_3\text{Cl}$, in which form it is often kept. Free phenylhydrazine rather than its salt is thought to

react with ketones, etc., but the hydrochloride is often used as a reagent in the presence of sodium acetate. Sodium acetate is used in large quantity; this decreases the acidity and allows free phenylhydrazine to form and to react with the carbonyl compound. Phenylhydrazine is an unstable substance and is easily oxidized. It reduces Fehling's solution and is converted into benzene, nitrogen and water.

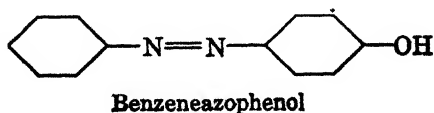
(2) **Formation of Diazoamino and Azo Compounds.** When a diazonium salt in strongly acid solution is treated with aniline, obviously nothing happens, because if the diazonium salt should react with aniline under these conditions, it would react with part of the original aniline while the diazonium salt is being formed. If, however, a large amount of sodium acetate (mildly alkaline) is added to the solution of the diazonium salt, aniline will react with the diazonium salt to form a compound which has been shown to have the following structure.



Under similar conditions dimethylaniline reacts with the diazonium salt after treatment with sodium acetate, to form a compound with the following structure, in which the $C_6H_5N_2$ group substitutes on the dimethylaniline in the *para* position.



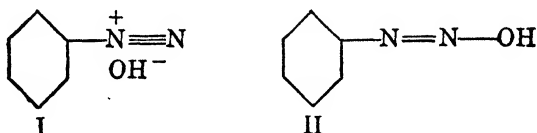
In the same way a solution of the diazonium salt, after treatment with alkali, will react with phenols to form



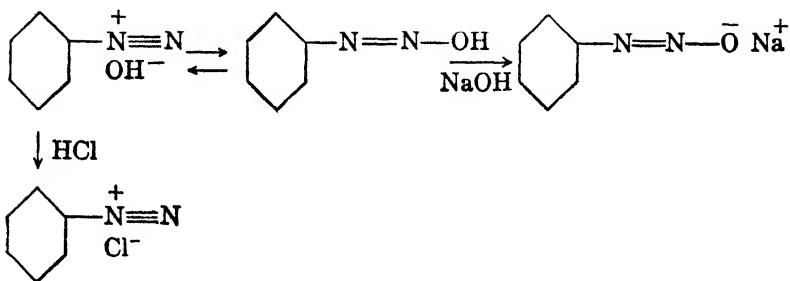
The reactions just mentioned are typical of a large number of reactions which are very important in the preparation of dye-stuffs and hence will be discussed more fully later. The term *coupling* is used to designate these reactions.

Tautomeric Relationships. The reactions which we have just cited are not only very important technically, but are interesting because they probably do not involve the diazonium salts as we have pictured them. The products formed are probably derived from substances with the Kekule type of structure.

The situation is explained on the basis of a tautomerism, in which one tautomer predominates in acid solution and the other predominates in alkaline solution. When a diazonium salt is treated with strong alkali, it is thought first to form the base (formula I) which, however, is unstable in this form and readily rearranges to form a compound with the structure II. This is a weak acid and is neutralized by the alkali.



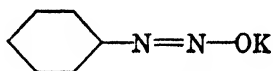
The situation which is thought to exist may be represented by the following scheme :



Thus as the condition of the solution changes from strong acidity to strong alkalinity, practically the entire material changes from one structure to the other. At points intermediate

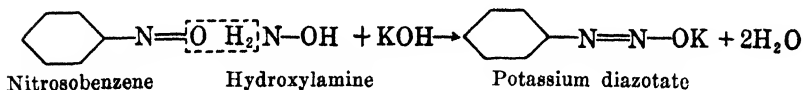
between extreme acidity and extreme alkalinity the two structures are thought to be present together in equilibrium. When sodium acetate, which is alkaline in reaction, is added to the solution of the diazonium salt, it favors the formation of the substance with the Kekule structure, and thus makes it possible for derivatives of this substance to be formed by reaction with aniline or phenol, etc. Reactions of the type that involve the substance with the Kekule structure are carried out in solutions which are alkaline or at most slightly acid.

Diazotates. As has already been mentioned, treatment of a diazonium salt with concentrated alkali results in the formation of a substance with the structure:



Potassium diazotate

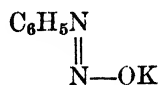
This is called *potassium diazotate*. It is also formed when *nitrosobenzene* and hydroxylamine react in the presence of alkali.



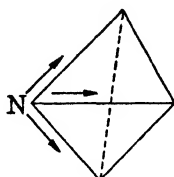
It can be obtained in crystalline form, but is quite unstable. When treated with a strong acid it is converted into the diazonium salt of the acid used.

Potassium diazotate reacts directly to give derivatives in which two nitrogen atoms connect two benzene nuclei, as in *p*-dimethylaminoazobenzene. When heated with a concentrated potassium hydroxide solution, potassium diazotate is converted into a stable isomer, which, except for its greater stability, is similar to potassium diazotate. The stable isomer can also be converted by strong acids into the diazonium salt.

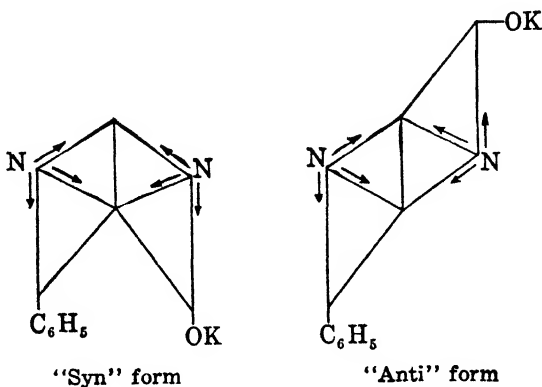
The existence of an isomeric compound is explained on the basis of a geometrical isomerism closely related to the *cis-trans* isomerism, and the two structures may be represented on a plane surface thus:



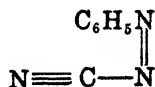
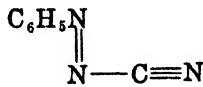
The three valences of the nitrogen atoms in such compounds are not symmetrically arranged in space since there is in addition to the three pairs of *shared* electrons, one pair of “*possessed*” electrons. The three valences may be pictured as directed along three edges of a tetrahedron, somewhat as in the following illustration



The spacial structure of the two diazotates may be diagrammatically represented as follows:



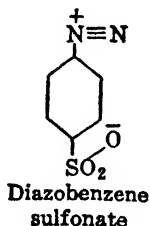
There are other “*syn*” and “*anti*” compounds analogous to the diazotates; for example, the benzenediazocyanides.

Benzenediazocyanide (*syn.*)Benzenediazocyanide (*anti.*)

One of these forms breaks down quite easily into benzonitrile and nitrogen while the other form does not. In the *syn* form the phenyl and cyanide groups are in close proximity, so that this structure is assigned to the form which yields benzonitrile readily.

In general, in the pairs of *anti* and *syn* isomers, one is quite stable in comparison to the other, and the *anti* arrangement is ascribed to the more stable isomer, sometimes without very definite proof. The stable form of potassium diazotate is thought to be the *anti* form, and the unstable form, which ordinarily forms first, is thought to be the *syn* form.

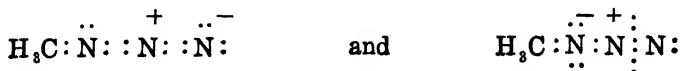
Diazobenzene Sulfonate. Sulfanilic acid, which is probably, as we have seen, in the form of an inner salt, can be diazotized with the resulting formation of the *diazobenzene sulfonate* which is the inner salt of a strong acid and a strong base.



Azides. When phenylhydrazine is treated with nitrous acid, it yields a substance known as *triazobenzene* (phenyl azide), $C_6H_5N_3$. The same reaction takes place when hydrazine itself, $NH_2 \cdot NH_2$, is treated with nitrous acid, forming the substance, HN_3 , which has acid properties and is sometimes known as *hydrazoic acid*. (Phenylhydrazides (p. 465) also yield the corresponding azides which may be useful reagents.) The azides resemble the diazonium salts in some respects, as they decompose readily, giving off nitrogen gas, and in the dry state may be explosive. See lead azide (p. 242).

Electron diffraction studies (p. 620) on triazomethane (methyl azide), CH_3N_3 , indicate that its structure involves a nitrogen chain as is also the case with the metal azides. The older formula involving a ring of three nitrogen atoms is incompatible with this evidence. The elec-

tronic structure of triazomethane is best described in terms of resonance between the following two (principal) structures:



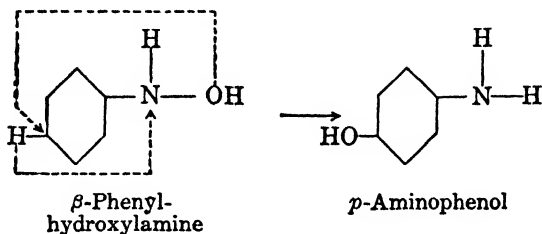
Intermediate Reduction Products of Nitrobenzene

It has been suggested that when nitrobenzene is reduced, aniline is the final but not the only product. There are other products which are intermediate between nitrobenzene and aniline. Some of these compounds are related to the diazo compounds, and because of this relationship all will be considered at this point.

Nitrosobenzene, $\text{C}_6\text{H}_5\text{NO}$, is undoubtedly formed in the reduction of nitrobenzene, but it cannot be prepared in this way since it is itself very easily reduced. It can be made by the oxidation of β -phenylhydroxylamine which may be prepared by reducing nitrobenzene under special conditions. (β -Phenylhydroxylamine is so named because it may be considered as derived from hydroxylamine, H_2NOH , by replacement of one of the β hydrogen atoms by the phenyl group. α -Phenylhydroxylamine has the hydrogen of the hydroxyl group replaced by the phenyl group.) β -Phenylhydroxylamine is obtained by the reduction of nitrobenzene with zinc dust in the presence of slight acidity such as exists in an ammonium chloride solution. It is a crystalline substance, which is very unstable and is oxidized and decomposed by contact with air. It reduces Fehling's solution readily.

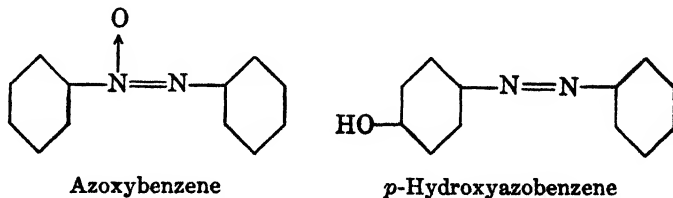
The reduction of the nitro group to give a hydroxylamine derivative has been utilized as a test for nitro compounds. The substance in question is treated with zinc dust under conditions that will form a hydroxylamine if the substance is a nitro compound, and the resulting material is tested with ammoniacal silver solution. If this is reduced, it is very good evidence that an aromatic nitro compound was originally present, for other substances do not yield reducing substances under these conditions.

In the presence of acids phenylhydroxylamine undergoes a rearrangement by which the molecule takes a more stable form. Trivalent nitrogen with one valence attached to oxygen or other non-metallic elements is an unstable combination and is likely to undergo rearrangement. In this case the hydroxyl group changes positions with the *para* hydrogen atom on the nucleus. This reaction again exemplifies the ease with which substitution takes place in the anilines and related compounds.



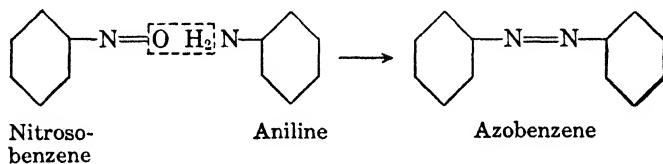
Azoxybenzene, $C_6H_5NO=NC_6H_5$, is best prepared by the reduction of nitrobenzene with sodium methoxide. Alcohols are easily oxidized in alkaline solutions because they exist partially in the form of their ionized sodium salts. While nitrobenzene is not a strong oxidizing agent it is strong enough to oxidize sodium methoxide to sodium formate, and is itself reduced. The reduction is accompanied by a condensation of two residues as the formula indicates.

The complete structure of azoxybenzene cannot be pictured satisfactorily without the designation of a coordinate valence between nitrogen and oxygen.



When heated this compound in common with β -phenylhydroxylamine undergoes a rearrangement to yield *p*-hydroxyazobenzene as indicated above. This shows a resemblance to amine oxides (p. 192) which can also give up their oxygen to reducing agents.

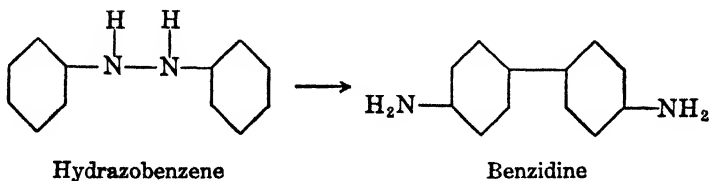
Azobenzene, $C_6H_5N=NC_6H_5$, has been so named for reasons of convenience. It is in a sense a *diazo* compound and as such might be called diazo di-benzene. However, the term *diazo* is reserved for those compounds in which only one aryl group is united to the $-N=N-$ group. It can be made by reducing azoxybenzene and thus represents another stage in the reduction of nitrobenzene. The reduction can be accomplished by heating an intimate mixture of azoxybenzene and iron filings. It has also been made from nitrosobenzene and aniline by condensation.



Azobenzene (az'o-běn-zēn) is a highly colored, red crystalline substance.

Hydrazobenzene, $C_6H_5NHNHC_6H_5$, can be prepared by the reduction of azobenzene with zinc dust in alkaline solution. It can also be made directly by the reduction of nitrobenzene in strongly alkaline solution. The latter method constitutes its commercial method of preparation. It may be regarded as α,β -diphenylhydrazine, but since it cannot undergo the reactions which are most typical of the hydrazines this name is not used. It can be oxidized to azobenzene even by the atmospheric oxygen when in alcoholic solution. It is a colorless substance.

When heated in the presence of acids a rearrangement of the groups in the molecules takes place as pictured below.



In this rearrangement the two nitrogen atoms part company, take two hydrogen atoms from the *para* carbon atoms, and the

two bereaved carbon atoms unite, with the result that the compound formed is much more stable. This rearrangement is an interesting one and important as well, for benzidine, the resulting compound, is an important dye intermediate.

It may be noted in concluding this discussion that in addition to aniline, nitrosobenzene, β -phenylhydroxylamine, azoxybenzene, azobenzene, and hydrazobenzene can each be made directly by the reduction of nitrobenzene or by the oxidation of one of the reduction products of nitrobenzene.

Diazo Compounds, Etc.

	Melting Point	Boiling Point
Diazoaminobenzene, $C_6H_5N_2NHC_6H_5$	96°	Expl.
Diazoxyhydroxyaminobenzene, $C_6H_5N_2N(OH)C_6H_5$	127°	
Triazobenzene, $C_6H_5N_3$		59° (12 mm.)
Azoxybenzene, $C_6H_5NO=NC_6H_5$	36°	dec.
Azobenzene, $C_6H_5N=NC_6H_5$	68°	295°-7
<i>o</i> -Azotoluene, $CH_3C_6H_4N=NC_6H_4CH_3$	55°	
<i>m</i> -Azotoluene, $CH_3C_6H_4N=NC_6H_4CH_3$	55°	
<i>p</i> -Azotoluene, $CH_3C_6H_4N=NC_6H_4CH_3$	144°	
Benzeneazomethane, $C_6H_5N=NCH_3$		Approx. 150°
Benzeneazoethane, $C_6H_5N=NC_2H_5$		Approx. 180°
<i>p</i> -Aminoazobenzene, $C_6H_5N=N(1)C_6H_4(4)NH_2$..	127.4°	> 360°
<i>m</i> -Aminoazobenzene, $C_6H_5N=N(1)C_6H_4(3)NH_2$..	57°	
2,4-Diaminoazobenzene, $C_6H_5N_2C_6H_3(NH_2)_2$	117°	
Hydrazobenzene, $C_6H_5NHNHC_6H_5$	131°	dec.
Phenylhydrazine, $C_6H_5NHNH_2$	19.6°	243.5°
Benzenediazonium chloride $C_6H_5N_2Cl$	dec.	
Benzenediazonium nitrate, $C_6H_5N_2NO_3$	expl.	
Benzenediazonium- <i>p</i> -sulfonate, $C_6H_4 \begin{matrix} \swarrow SO_2O \\ \searrow N \equiv N \end{matrix}$	dec.	

PROBLEMS

1. How much nitrogen gas measured at standard conditions would be evolved by treatment of 0.5 gram of *o*-toluidine with an excess of nitrous acid?

2. How could *m*-dichlorobenzene be made from benzene using the diazo reactions?

3. Suppose that *p*-phenylenediamine is diazotized, and is then treated with dimethylaniline in the same way as described for aniline. what is the structure of the resulting compound?

4. What inorganic compounds are known which are intermediate in stage of oxidation between nitric acid and ammonia?

5. Phenylhydrazine is made to react with an unknown compound. The molecular weight determination on the hydrazone shows it to have a molecular weight of 134. What is the molecular weight of the unknown compound?

6. How much Fehling's solution (p. 355) should be required to oxidize 2.5 grams of phenylhydrazine?

7. If the three hydrogen atoms of ammonia occupy positions that are equidistant and symmetrical in space, what would be their spacial arrangement? Would *anti* and *syn* isomers be possible if this were the case?

8. The existence of at least six hydrides of nitrogen is mentioned on p. 4. What are they? Two of these are salts.

9. A method of quantitative determination of the number of carbonyl groups present in a compound is based upon the following procedures. A known amount of the substance is treated with a known amount (an excess) of phenylhydrazine. The resulting mixture is then oxidized with Fehling's solution and the amount of nitrogen gas evolved is measured. Only the free phenylhydrazine is oxidized by Fehling's solution by the procedure. Suppose that 0.2 gram of acetone is treated in the manner described, with 0.5 gram of phenylhydrazine, and the mixture oxidized; how much nitrogen, measured at standard conditions, would be evolved?

CHAPTER XXVIII

PHENOLS

Those compounds which have the hydroxyl group attached to a carbon atom of the benzene nucleus are called *phenols* (s. fě'nōl). Although they are in reality a type of alcohol, they show characteristic differences which justify the use of a special name.

Phenol (carbolic acid), C_6H_5OH , is obtained from coal tar of which it is an important constituent and from petroleum. It is also manufactured on a large scale by the fusion of sodium benzenesulfonate with sodium hydroxide (p. 444) or the high temperature hydrolysis of chlorobenzene (p. 430). Since these methods are not suitable for elementary laboratory work and require more or less special equipment, the most common method of laboratory preparation consists in decomposing benzenediazonium chloride by heating in water solution.

Phenol is a type of tertiary alcohol, but due to the attachment of the hydroxyl group to the nucleus, it has some peculiar properties. The same effect of the phenyl group which decreases the base-forming property of aniline *increases* acid properties so that phenol has distinct acid properties in distinction to the alcohols which are weaker in acid properties than water. Phenol is a weak acid, however, and can be liberated from its salts by carbonic acid. It is able to affect some indicators, but has no effect on those which are less sensitive to weak acids.

Poisonous Properties. The weak acid property of phenol may seem contrary to the common knowledge that phenol is "strong" in its physiological action. The poisonous property is not due to the acid property, however, but to other factors. In concentrated form phenol is hygroscopic, and caustic, and will burn tissues, and cause blisters. In dilute form it is poisonous at least partly due to its action in precipitating and coagulating proteins as well as other labile colloidal systems, in which respect its action bears some resemblance to that of the heavy acids

(p. 318). The understanding of exactly how a poison acts involves not only a thorough knowledge of the characteristics of poison but also involves a knowledge of the characteristics of protoplasm with which it reacts.

The complexity of the situation is illustrated by the striking fact that the higher homologs of phenol are distinctly less poisonous *toward higher animals* than is phenol itself. Toward bacteria and certain other micro-organisms, however (and these do not all behave uniformly), the higher homologs are much more poisonous than is phenol. For this reason homologs of phenol (and other phenols) are much more effective germicides and safer to use than phenol. If we understood the chemistry of living matter as well as we do the chemistry of phenol we could describe more accurately its physiological action.

Formation of Substituted Phenols. The presence of the hydroxyl group attached to the benzene nucleus has an effect similar to that of the amino group, in that the *ortho* and *para* hydrogen atoms are very easily substituted. Treatment of phenol with bromine water produces symmetrical tribromophenol. (Note similarity to aniline, p. 449.) *Ortho* and *para* nitrophenols are formed when phenol is treated at ordinary temperature with about 20 per cent nitric acid. Other derivatives also form readily.

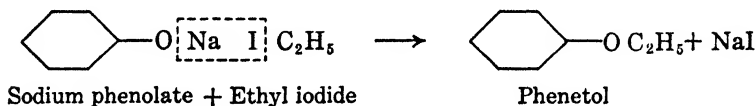
Esters of Phenols. Phenols resemble aliphatic alcohols in several respects. By the action of acetic anhydride or acetyl chloride on phenol, *phenyl acetate*, $C_6H_5OCOCII_3$, is formed. This substance is the mixed anhydride of phenol and acetic acid, and in conformity to the general principle already noted (p. 162), this substance is more readily and completely hydrolyzed than the ordinary esters as it is the anhydride of the more strongly acidic phenol. It is readily broken down by heating with water, and is not prepared by the action of acetic acid on phenol.

Chlorobenzene is an ester of hydrochloric acid and phenol but cannot readily be made by the interaction of these substances, because the phenyl group holds the oxygen of the hydroxyl group tightly. Chlorobenzene and other phenyl halides might be expected to behave like phenyl acetate and hydrolyze readily, because they too are esters of more strongly acidic alcohols (phenols).

The differences in structure between phenyl halides and other esters are too great, however, to make a direct comparison possible. The phenyl halides (as well as many other phenyl combinations) are extraordinarily stable; unlike phenyl acetate above, they cannot undergo hydrolysis without breaking the attachment to the phenyl group. When various halogen substitution products of benzene are compared with each other they conform to the principle noted above. For example, the introduction of a nitro group into a phenol makes it much stronger in acid properties, and the corresponding halogen esters are much more easily hydrolyzed. See also the case of picryl chloride (p. 481).

Triphenyl phosphate, $(C_6H_5O)_3PO$, and *tri-o-cresyl phosphate*, $(CH_3C_6H_4O)_3PO$, are phenolic esters which are used like camphor as plasticizers in the manufacture of celluloid-like plastics (p. 381).

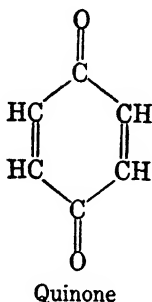
Ethers of Phenols. Phenols, like the alcohols, form ethers as indicated in the following example.



The methyl and ethyl ethers of phenol are known as *anisol* and *phenetol* respectively. *Diphenyl ether* (diphenyl oxide) is available as a by-product of the production of phenol by the hydrolysis of chlorobenzene using sodium hydroxide (p. 430). It is used in the manufacture of perfumery.

Oxidation of Phenols. Contrary to what might be expected from the fact that phenol is a type of tertiary alcohol, it is rather susceptible to oxidation. In fact some of the homologs of phenol (cresols, etc.) reduce Fehling's solution appreciably and certain di- and triphenols are among the most easily oxidized organic compounds. Phenols probably exist in tautomeric forms (see p. 488) and this may have something to do with their ease of oxidation, though this seems doubtful. The ease of oxidation of phenols is undoubtedly connected with the fact that substitution, especially in the *para* and *ortho* positions, is greatly facilitated by the hydroxyl group (p. 440). Phenols resemble anilines both in ease of substitution and ease of oxidation. Oxidation in

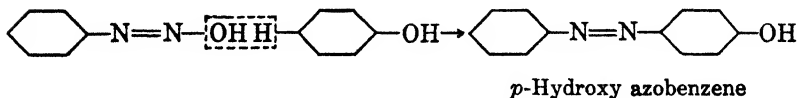
phenols is known to be facilitated in the *para* position because on oxidation with dichromate in dilute acid solution phenol yields as one of the products *quinone* which has the structure indicated below. (The substance will be studied in more detail later.)



According to the Claus benzene structure the *para* bond is broken on oxidation and therefore these two carbon atoms are attacked.

The oxidation products of phenol are various and complicated. When certain oxidizing agents are used such as ferric chloride, highly colored compounds are formed by the oxidation and if the test is carried out in a definite way these colors may be used for their identification. Different substituted phenols often give different colors under like conditions, and so may be differentiated.

Other Reactions of Phenols. Phenol reacts with diazonium salts, after their rearrangement in alkaline solution, to give azo compounds, as is shown in the following simple case.



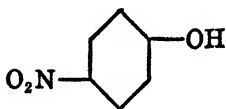
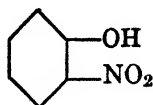
The entering group goes principally to the position *para* to the hydroxyl group. Substituted phenols as well as phenol itself undergo this type of reaction and the compounds formed in many cases are important dyestuffs.

Phenol also undergoes very complex condensation reactions with formaldehyde in the presence of alkali. The resinous material first formed is soluble and melts readily, but is polymerized by heat to an infusible, insoluble solid "resinoid." This material, which may be made in different ways, is used for insulation materials, phonograph records, umbrella handles, fountain pen barrels, etc. The composition of the material is very complex and very incompletely known. "Bakelite" is a trade name under which materials of this type are sold.

Homologs of Phenol. Many closely related compounds occur with phenol in coal tar and petroleum. The *cresols* or *cresylic acids*, $\text{HOC}_6\text{H}_4\text{CH}_3$, are the most important and all three homologs occur in something like equal amounts. The cresols are the most abundant of the phenols in petroleum. A mixture of the three cresols is widely used as a disinfectant (Lysol) and in the refining of lubricating oils. *Xylenols*, $\text{HOC}_6\text{H}_3(\text{CH}_3)_2$, and higher homologs are also present in coal tar and petroleum. *Trimethyl phenol* (2,3,6) obtained from petroleum is used in the synthesis of Vitamin E (p. 599). *Thymol*, *methyl isopropyl phenol* (3,6), occurs in various essential oils of vegetable origin and gets its name from its occurrence in oil of thyme. It is used as a disinfectant and in medicine. *Carvacrol*, *methyl isopropyl phenol* (2,5), as the name shows, is an isomer of thymol. It also occurs in essential oils and is used in medicine. It will be noted that both thymol and carvacrol are derivatives of cymene (p. 419).

Substitution Products of Phenol. Mention has already been made of the ease with which substitution takes place when phenol is treated with various reagents which react with benzene.

Nitrophenols. When the nitration of phenol is carried out with diluted nitric acid *o*- and *p*-nitrophenols are formed.

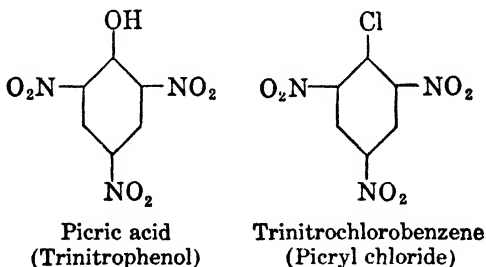
*p*-Nitrophenol*o*-Nitrophenol

Of the two, the *ortho* compound has an appreciable vapor pressure at the temperature of boiling water and hence is volatile with steam. It has a distinct odor; this would not be possible if it were non-volatile. The *para* compound is neither volatile with steam nor does it have an odor.

If *p*-nitrophenol is converted into its ethyl ether, reduced to an amine, and the amine is acetylated, **phenacetin** is produced. This drug is similar to acetanilide, which it resembles in structure, though it is said to be less dangerous to use. It is used in headache tablets, and in the treatment of neuralgia, etc.

Dinitrophenols in general and especially the dinitrocresols are used extensively as contact insecticides.

Picric Acid. When the nitration of phenol is carried out in the presence of concentrated sulfuric acid, sulfonic acids have been shown to be formed as intermediate products. These are unstable under these conditions, however, and the final product contains three substituted nitro groups. It is *trinitrophenol*, or *picric acid*.



The nitro groups increase the acid properties of the phenol, and in picric acid the acid property is comparable with the strong acids.

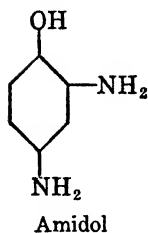
When treated with phosphorus pentachloride, picric acid yields picryl chloride or *sym. trinitrochlorobenzene*. This substance is the hydrochloric acid ester of the picric acid (a phenol). However, picric acid has strong acid properties and the compound resembles the acid chlorides of stronger acids. It is easily hydrolyzed and reacts with ammonia (ammonolysis) to give *picramide*, which also resembles the acid amides in that it can be hydrolyzed readily. Use has been made of the ease of hydrolysis

of sym. trinitrochlorobenzene for the manufacture of picric acid. Chlorobenzene is first nitrated and the trinitrochlorobenzene is then hydrolyzed to picric and hydrochloric acids.

Picric acid contains both oxidizing and reducing groups, and is, in the proper form, a valuable explosive. It is the principal ingredient of *lyddite*, a military explosive. Ammonium picrate is also used as an explosive. Picric acid is a yellow crystalline substance, which has been used as a dye for wool or silk but is no longer used for this purpose. When treated with bleaching powder the benzene nucleus is broken and picric acid yields, among other products, *chloropicrin*, CCl_3NO_2 (p. 216). This substance has been used in gas warfare.

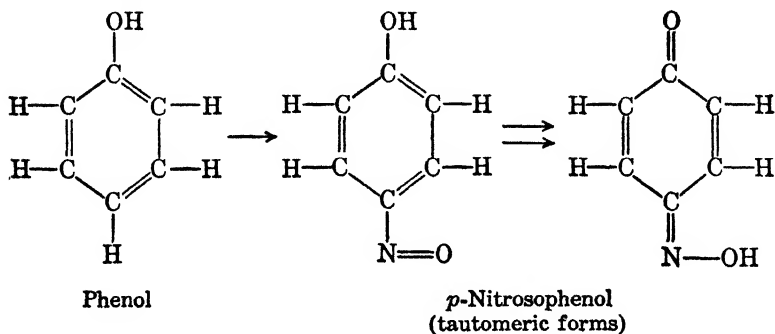
Picric acid has the property of uniting with aromatic hydrocarbons, benzene, naphthalene and anthracene, to form crystalline addition compounds. It forms a colorless crystalline compound with benzene, $\text{C}_6\text{H}_6 \cdot \text{C}_6\text{H}_2(\text{OH})(\text{NO}_2)_3$. The character of the valences between the different kinds of molecules in these compounds is probably of the same general nature as is involved in water of crystallization, and cannot be represented by the same symbolism as is used for ordinary valences. There is probably a relationship between this ability to form double compounds and the unsaturation which resides in the benzene nucleus. Picric acid forms salts with various basic compounds which are often useful as means of identifying the bases.

Amino phenols can be made by the reduction of nitrophenols and also in other ways. All three isomeric amino phenols are useful substances but the *para* compound is probably the most important. It can be made by the reduction of *p*-nitrophenol or by reducing nitrobenzene under conditions which first produce β -phenylhydroxylamine. This rearranges to give *p*-aminophenol (p. 472). *p*-Aminophenol is used under the name of *rhodinal* as a photographic developer. *p*-Methylaminophenol in the form of the sulfate is a very important photographic developer known as *metol*. *Amidol* is another photographic developer of a similar sort, which is made by reducing the corresponding dinitrophenol.



A photographic developer must be a very easily oxidized substance, and this is true of all of the developers mentioned; they reduce Fehling's solution and ammoniacal silver solution. There are numerous derivatives of the phenols which are very easily oxidized by these solutions so that the reduction of Fehling's solution or ammoniacal silver solution cannot be used as a test for aldehydes or for hydroxy ketones unless derivatives of phenols are known to be absent.

The readiness with which phenols form substitution products is illustrated by the fact that **phenol sulfonic acids** are easily formed from phenol and sulfuric acid, at ordinary temperature. Another reaction, which also illustrates this property and at the same time shows the resemblance between phenols and anilines, is that between phenol and nitrous acid. Phenol reacts with nitrous acid just as dimethylaniline does. The nitroso group substitutes in the *para* position.

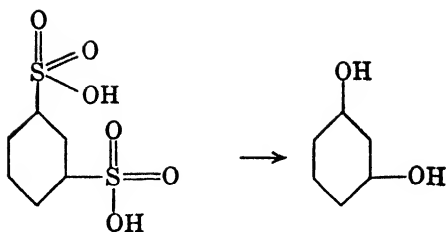


***p*-Nitrosophenol** which is formed undergoes reversible tautomeric change as indicated. This tautomerism is one of those which is well established and will be mentioned later.

Dihydroxybenzenes, *o*-Dihydroxybenzene is known as **catechol** (also *pyrocatechin* and *pyrocatechol*). It was first obtained by distillation of a plant gum known as *catechin*, and derived its names from this material. By treatment of phenol with chlorine *o*-chlorophenol may be prepared. Due to the influence of the hydroxyl group, this substance can be hydrolyzed by the use of alkali, and from it catechol is prepared. It is an easily oxidized substance, and reduces Fehling's solution markedly in the cold. Its lead salt is precipitated by adding lead acetate to its solution and its calcium salt is precipitated by ammoniacal calcium chloride solution. These reactions, especially the former, take place with substituted *o*-dihydroxybenzenes as well, but do not take place with the *m*- and *p*-dihydroxybenzenes.

Catechol (kät'é-chöl) is used as a photographic developer and for the manufacture of its methyl ether **guaiacol**, $\text{HOC}_6\text{H}_4\text{OCH}_3$, and for the manufacture of **adrenaline** (äd-rën'ä-lën), $(\text{HO})_2\text{-C}_6\text{H}_3\text{CHOHCH}_2\text{NHCH}_3$. The latter substance was first obtained from the adrenal glands and is physiologically very active. It is used in medicine, and may now be obtained synthetically. It has an asymmetric carbon atom in its structure and thus exists in *d*- and *l*-forms. The *l*-form is much more active physiologically and is separated from the inactive synthetic mixture by combining with *d*-tartaric acid, and separating the two salts by crystallization (p. 279).

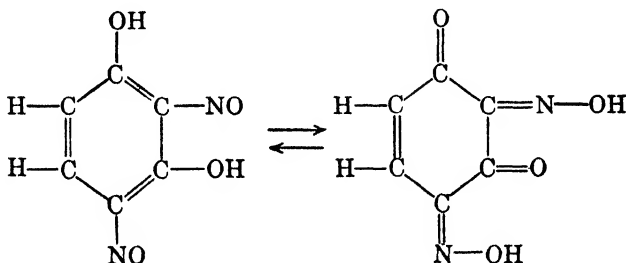
m-Dihydroxybenzene is called **resorcinol**. It gets its name from the fact that it is produced by fusion of certain resins with sodium or potassium hydroxide. It seems that in an alkaline condition at high temperature the hydroxyl groups are most stable in the *meta* position for when compounds with the hydroxyl groups in *ortho* or *para* positions are fused with alkali, rearrangement to the *meta* position takes place. For instance, benzene *p*-disulfonate on fusion with alkali first produces *p*-dihydroxybenzene which then rearranges to form resorcinol. Resorcinol is made technically by fusing benzene *m*-disulfonic acid (which may contain some of the *para* compound) with alkali.



Benzene
m-disulfonic acid¹

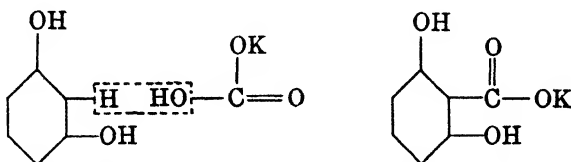
Resorcinol

Resorcinol reduces Fehling's solution very slowly at the boiling point but has no effect at room temperature. It is very easily chlorinated, brominated or nitrated to form tri-substitution products. It reacts with nitrous acid to form 2,4-dinitrosoresorcinol, which like *p*-nitrosophenol exists in two forms.



2, 4-Dinitrosoresorcinol

The extreme ease with which substitution may take place in a phenol is illustrated by the fact that a carboxyl group may be substituted by treatment of resorcinol with potassium bicarbonate, as shown below.

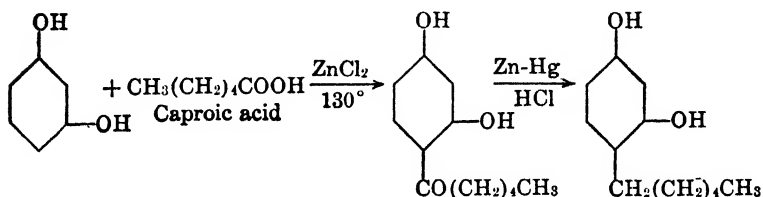


Resorcinol + Potas-
sium bicarbonate

Salt of 2, 6-dihy-
droxybenzoic acid

¹ For the nature of the S=O bond see page 227.

Resorcinol also undergoes condensation with diazonium salts like the other phenols, and dyes are produced. Resorcinol has application in medicine as an antipyretic, antispasmodic and antiseptic. **4-*n*-Hexyl resorcinol** ("Caprokol") is widely used as an antiseptic and in the treatment of hookworm. It is prepared from resorcinol by the following reactions:



This is a Friedel and Crafts type condensation but resorcinol is so easily substituted that an acid chloride may be used along with the moderately active zinc chloride as a catalyst.

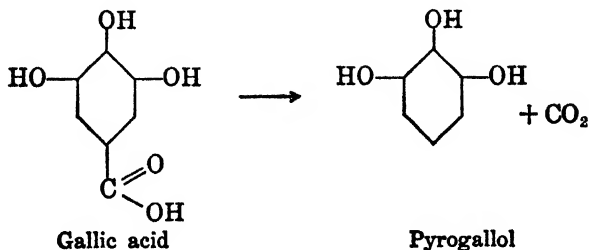
Quinol. *p*-Dihydroxybenzene is commonly known as *hydroquinone* and sometimes as *hydroquinol*, though a better name is quinol. It is produced by the hydrolysis of certain glucosides (p. 382). Its technical preparation involves the oxidation of aniline to form *quinone*, $\text{C}_6\text{H}_4\text{O}_2$, and the subsequent reduction of the quinone to hydroquinone. Quinol is a very strong reducing agent and is widely used as a photographic developer. Like all of the phenols it is much more easily oxidized in alkaline than in acid solution. This is true of hydroxy compounds generally. The alkaline solutions of quinol as well as some of the other phenols turn dark on exposure to the air, due to oxidation. For use as photographic developers, it is necessary that the substances be so easily oxidized that the silver bromide particles after exposure to light are able to oxidize them. This ease of oxidation is only brought about by using the developer in alkaline solution. The alkalinity must not be too high, partly because high alkalinity causes a softening of the gelatin. The desired alkalinity is generally obtained by the use of sodium carbonate, though the sulfites used also increase alkalinity.

The fact that *para* and *ortho* diphenols are especially strong reducing agents while the *meta* compounds are much weaker, is reasonable in light of the probable existence of *para* bonds in the benzene formula (p. 414) because in both *ortho* and *para* compounds (but not in *meta*) the carbon atoms holding oxygen are connected.

Quinol is one of the most effective **antioxidants**. Like many other easily oxidized substances its presence in unsaturated oils for example retards the rate of oxidation by air. Such oxidation is probably due to the formation of peroxides which is prevented by the antioxidant. The antioxidant probably acts catalytically but also may itself be actually oxidized. Very small amounts of natural antioxidants are present in natural fats and oils and play an important rôle in prevention of the development of rancidity and the destruction of certain reactive vitamins which are present. Peroxides catalyze the polymerization of unsaturated compounds and antioxidants by preventing peroxide formation thus may be used to retard polymerization. Antioxidants are introduced into rubber where they prevent ageing and can be added to cracked gasoline where they prevent polymerization and gum formation on storage.

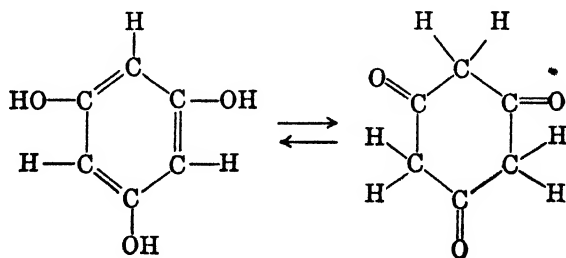
Orcinol or *orcin* is 1,3,5-dihydroxytoluene. It is used to some extent as a laboratory reagent.

Trihydroxybenzenes. Of the three trihydroxybenzenes the only one of technical importance is **pyrogallol** (*pyrogallic acid*) in which the hydroxyl groups are vicinal. It is made by the heating of gallic acid. The reaction is similar to that used in the preparation of methane from sodium acetate except that it is not necessary to heat with alkali.



Toward different oxidizing agents different phenols behave somewhat differently. Pyrogallol in alkaline solution is particularly easily oxidized by oxygen gas which it will remove quantitatively and rapidly from a given sample of a gas. It is therefore used in strongly alkaline solution in gas analysis. Pyrogallol also reduces Fehling's solution readily and produces a silver mirror from an ammoniacal silver solution, without warming. It is used in the preparation of a few dyes, but its principal use is that of a photographic developer. It has been a standard developer for negatives for many years. The methyl ethers of pyrogallol are present in large quantity in wood tar.

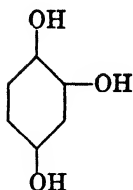
Phloroglucinol, *sym.* trihydroxybenzene, is only of theoretical importance. It can be made by fusing symmetrical benzene trisulfonic acid with alkali. It is a reducing agent but is much weaker than pyrogallol. Interest in this substance centers around its structure. It acts like a trihydroxyphenol in that it forms salts, tri-ethers, and tri-esters. On the other hand it acts like a tri-ketone in that it reacts with hydroxylamine to form a tri-oxime (p. 106). The reactions indicate that phloroglucinol is a tautomeric mixture of substances with the following structures.



Phloroglucinol

The clear evidence in this case implies that in other phenols a similar tautomerism exists. In other cases, however, the evidence is not always definite.

Hydroxyquinol is the unsymmetrical trihydroxybenzene with the structure :



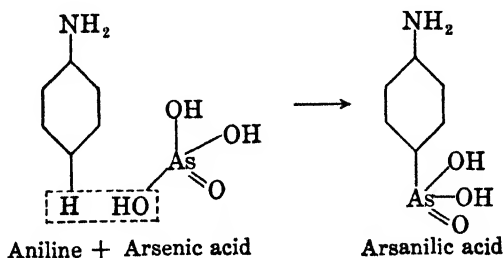
Hydroxyquinol

It can be made by fusing quinol with an alkali, but quinol is expensive and the method is unsatisfactory so that the compound is of little importance. If it were obtainable cheaply, it would no doubt find use as a photographic developer.

Phenols with as high as six hydroxyl groups attached to the nucleus are known but are not of special theoretical or practical interest.

Certain arsenic derivatives may be made from phenol which are of much importance, because of their application in the cure of diseases caused by protozoa. One of the most important is *salvarsan* which has been used successfully in the treatment of syphilis. This substance was discovered by Ehrlich² who made a long and systematic search for suitable arsenic compounds which would kill the protozoa without poisoning the host. This compound was number 606 in the series of compounds investigated by him and is sometimes called "606" for this reason.

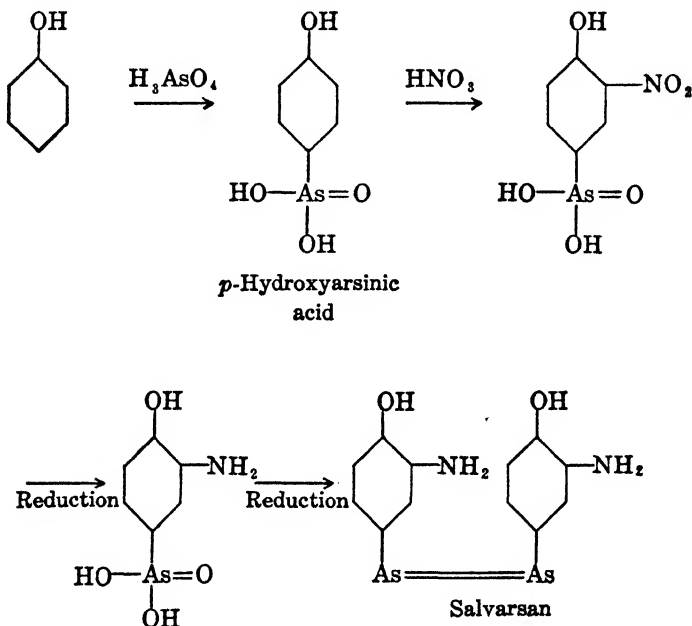
Aniline when heated with arsenic acid at about 200° forms *arsanilic acid*. This reaction illustrates the ease of substitution in aniline and is analogous to the formation of sulfanilic acid.



² Paul Ehrlich (1854-1916) was for a number of years Director of the Royal Institute for Experimental Therapy in Frankfurt. Salvarsan was discovered about 1911.

The sodium salt of arsanilic acid is known as *atoxyl* and was known by Ehrlich to be efficient in destroying the parasites but was also somewhat poisonous to the patient. It was found during the course of the investigation that it is trivalent arsenic that is effective in destroying the parasites and that the effectiveness of *atoxyl* is due to its conversion in the body into trivalent arsenic compounds.

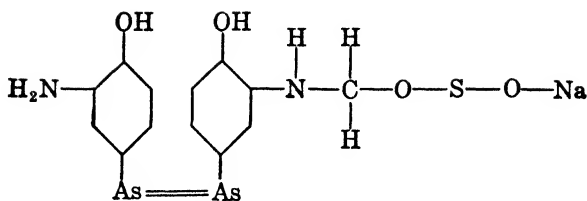
Salvarsan is related to *atoxyl* and may be made as indicated below:



The formation of *p*-hydroxyarsinic acid illustrates the ease of substitution in phenols. This substance can also be made by diazotizing arsanilic acid and decomposing with water. The reduction of the nitro compound takes place in two stages the latter of which is analogous to the formation of azobenzene by the reduction of nitrobenzene.

Neosalvarsan is a derivative of salvarsan which has advantages, the most important of which is its greater solubility. It has the structure indicated below and is number 914 in Ehrlich's series of compounds.³

³ As the formula indicates it is a derivative of $\text{S}(\text{OH})_2$, a hypothetical acid (sulfoxylic acid). For further material on arsenic compounds consult Gilbert T. Morgan, "Organic Compounds of Arsenic and Antimony," Longmans, Green & Co.



Neosalvarsan

(3, 3'-Diamino-4, 4'-dihydroxyarsenobenzene-*N*-methylene sulfinate)

Phenols and Phenol Ethers

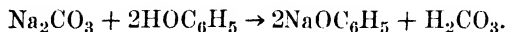
	Melting Point	Boiling Point
Phenol (carbolic acid), $\text{C}_6\text{H}_5\text{OH}$	41°	183°
<i>o</i> -Cresol, $\text{CH}_3\text{C}_6\text{H}_4\text{OH}$	31°	191°
<i>m</i> -Cresol, $\text{CH}_3\text{C}_6\text{H}_4\text{OH}$	11.2	202°
<i>p</i> -Cresol, $\text{CH}_3\text{C}_6\text{H}_4\text{OH}$	36°	202°
Thymol, $\text{C}_6\text{H}_7(6)\text{C}_6\text{H}_5\text{OH}(1)\text{CH}_3(3)$	49.6°	231.8°
Carvacrol, $\text{C}_6\text{H}_7(5)\text{C}_6\text{H}_5\text{OH}(1)\text{CH}_3(2)$	0°	238°
Anisol, $\text{C}_6\text{H}_5\text{OCH}_3$	-37.8°	155°
Phenetol, $\text{C}_6\text{H}_5\text{OC}_2\text{H}_5$	-30.2°	172°
Diphenyl ether, $\text{C}_6\text{H}_5\text{OC}_6\text{H}_5$	28°	259°
Pyrocatechol (<i>o</i>), $\text{C}_6\text{H}_4(\text{OH})_2$	104°	245°
Guaiacol (<i>o</i>), $\text{C}_6\text{H}_4(\text{OH})\text{OCH}_3$	31.3°	205°
Veratrol (<i>o</i>), $\text{C}_6\text{H}_4(\text{OCH}_3)_2$	23°	207°
Homopyrocatechol, $\text{CH}_3(1)\text{C}_6\text{H}_3(\text{OH})_2(3,4)$	65°	251.2°
Rosorcinol (<i>m</i>), $\text{C}_6\text{H}_3(\text{OH})_3$	110°	280°
Orcinol, $\text{CH}_3(1)\text{C}_6\text{H}_3(\text{OH})_2(3,5)$	107°	289°
Cresorcinol, $\text{CH}_3(1)\text{C}_6\text{H}_3(\text{OH})_2(2,4)$	104°	269°
Hydroquinone (<i>p</i>) (quinol), $\text{C}_6\text{H}_4(\text{OH})_2$	169°	285°
Methyl hydroquinone, $\text{CH}_3\text{OC}_6\text{H}_4\text{OH}$	53°	247°
Dimethyl hydroquinone, $\text{C}_6\text{H}_4(\text{OCH}_3)_2$	56°	213°
Hydrotoluquinone, $\text{CH}_3(1)\text{C}_6\text{H}_3(\text{OH})_2(2,5)$	124°	
Pyrogallol, $\text{C}_6\text{H}_3(\text{OH})_3(1,2,3)$	132°	293°
Pyrogallol trimethyl ether, $\text{C}_6\text{H}_3(\text{OCH}_3)_3$	47°	241°
Phloroglucinol, $\text{C}_6\text{H}_3(\text{OH})_3(1,3,5)$	218°	sub. dec.
Phloroglucinol trimethyl ether, $\text{C}_6\text{H}_3(\text{OCH}_3)_3$	52°	255°
Hydroxyquinol, $\text{C}_6\text{H}_3(\text{OH})_3(1,2,4)$	140.5°	

PROBLEMS

1. Compare the results obtained by dissolving sodium methoxide in water with those obtained by dissolving sodium phenoxide in water.
2. How would you expect the acid strengths of pyrogallol and quinol to compare with that of phenol? Why?
3. Should the halogen substitution products of phenol be expected to be weaker or stronger in acid properties than phenol itself?

4. Tertiary alcohols lose water rather readily to yield unsaturated hydrocarbons. Would you expect phenol to react in an analogous manner?

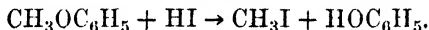
5. Will the reaction represented by the following equation take place? Why?



6. Write the full structural formulas for thymol, carvacrol, phenacetin, metol.

7. Write the formula for a tautomeric form of phenol.

8. Methoxy groups are quantitatively determined by heating the compounds with hydriodic acid under such conditions that the methyl iodide formed is caught in alcoholic silver nitrate solution. Suppose anisol is treated in this way, how much silver iodide would theoretically be obtained from a 0.2 gram sample? What percentage methoxy is anisol?



9. Suppose that hydrochloric acid acts like hydriodic acid (problem 8). Why could it not be used in the determination of methoxy?

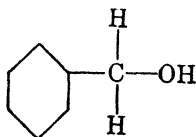
10. Diphenyl ether can be prepared by heating phenol with zinc chloride. Why would this reaction be easier to carry out than a similar one to prepare ordinary ether? Note the boiling points of the substances involved.

CHAPTER XXIX

AROMATIC ALCOHOLS, ALDEHYDES AND KETONES

When hydroxyl groups are attached to carbon atoms of the benzene nucleus, the compounds have distinct acid properties, and other distinctive characteristics, and are called phenols. When a hydroxyl group is attached to a carbon atom in a "side chain," the substance has the properties common to aliphatic alcohols, and is called an aromatic alcohol, and not a phenol.

Benzyl alcohol ($C_6H_5CH_2-$ is the benzyl (bĕn'zil) group) is isomeric with the cresols, from which it can easily be distinguished by its lack of distinct acid properties.



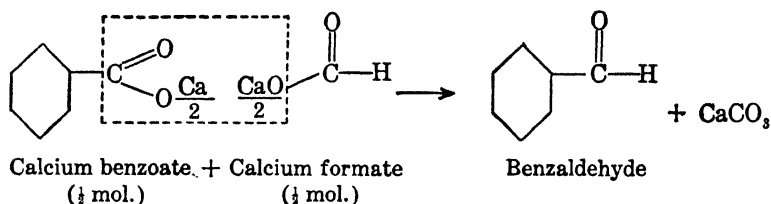
Benzyl alcohol

It can be prepared by the hydrolysis of benzyl chloride which is obtained by chlorinating toluene (p. 434). Due particularly to its high molecular weight benzyl alcohol has a high boiling point (200°), and is only moderately soluble in water. Benzyl cellulose has been mentioned (p. 375). Benzyl esters find some use in perfumery. Other aromatic alcohols are similar in general properties to benzyl alcohol, but are not of sufficient importance to justify individual discussion here.

Benzaldehyde

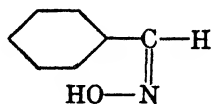
Benzaldehyde, C_6H_5CHO , or oil of bitter almonds, is important because of its use in flavoring, and perfumery, and in the manufacture of dyes. It is formed along with hydrocyanic acid and glucose by the action of the enzyme *emulsin* on the glucoside *amygdalin*. The hydrolysis of the glucoside can also be brought about by heating with acids.

Similarity to Aliphatic Aldehydes. The preparation of benzaldehyde can be accomplished in a number of ways which show its resemblance to the aliphatic aldehydes. It can be made by the oxidation of the primary alcohol, benzyl alcohol, $\text{C}_6\text{H}_5\text{CH}_2\text{OH}$, or by the hydrolysis of benzal chloride, $\text{C}_6\text{H}_5\text{CHCl}_2$, or by the dry distillation of a mixture of calcium benzoate and calcium formate.

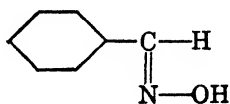


Like the aliphatic aldehydes, benzaldehyde is easily oxidized under certain conditions and gives the silver mirror test. It also forms addition products with hydrocyanic acid, sodium bisulfite and ammonia (at low temperature), and reacts with hydroxylamine, phenylhydrazine, semicarbazide (p. 106).

Oximes. When benzaldehyde reacts with hydroxylamine, an oxime is formed which is thought to have the structure indicated below (I). When this is treated with hydrochloric acid it changes over into an isomeric substance to which structure II is assigned.



I
Anti Benzaldoxime

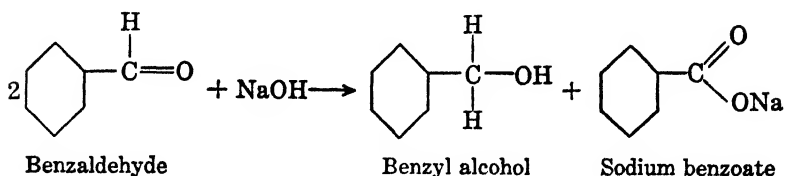


II
Syn Benzaldoxime

Characteristic Differences; Cannizzaro's¹ Reaction. In the presence of strong alkalis benzaldehyde does not polymerize as do most aliphatic aldehydes, but reacts like formaldehyde (p.

¹ Discovered by Stanislo Cannizzaro (1826-1910), an Italian chemist of note. He is famous because in 1858 he published a remarkable booklet discussing current views on atomic and molecular weights, which did much to clear up the existing confusion. He was Professor in Genoa, Palermo and Rome.

98). By intermolecular oxidation and reduction, sodium benzoate and benzyl alcohol are formed.



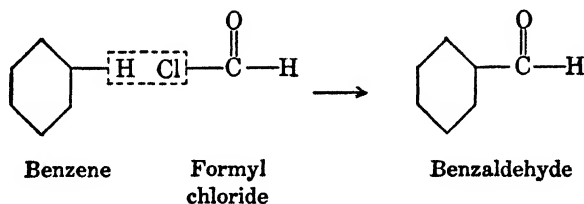
Oxidation. Benzaldehyde is on the whole much less easily oxidized than the aliphatic aldehydes. Though it gives the silver mirror test, it does not reduce Fehling's solution. Even more striking is the fact that under some conditions benzaldehyde is less easily oxidized than benzyl alcohol. By choice of oxidizing agents (nitric acid or other nitrates may be used) it is possible to prepare benzaldehyde by the oxidation of benzyl alcohol. It will be remembered that in the oxidation of ethyl alcohol, acetaldehyde may be recovered only because it is very volatile and escapes from the oxidizing solution. This is not the case in the oxidation of benzyl alcohol for benzaldehyde boils at 179° and does not leave the oxidizing mixture. Benzaldehyde may also be prepared by the oxidation of benzyl chloride or even by the oxidation of toluene directly with chromyl chloride, CrO_2Cl_2 , in carbon disulfide solution. Under these conditions benzaldehyde forms an insoluble compound with the excess of the chromyl chloride. From this compound the benzaldehyde may be recovered. Benzaldehyde may also be made by the partial oxidation of toluene by manganese dioxide in the presence of sulfuric acid kept at about 40° . These methods of preparation indicate how under some conditions benzaldehyde is stable toward oxidizing agents.

On the other hand benzaldehyde is more readily oxidized by atmospheric oxygen than the aliphatic aldehydes. As a result, if benzaldehyde is left exposed to the air for some time, it is converted into a mass of crystals of benzoic acid. This is an auto-oxidation due to the intermediate formation of an unstable

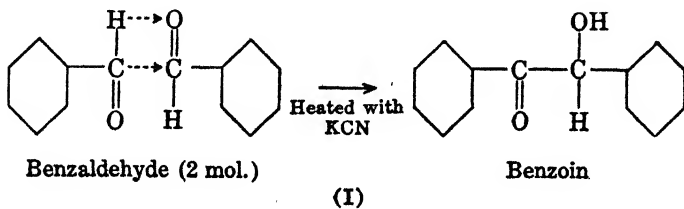
peroxide with the formula $\text{C}_6\text{H}_5\text{C}(=\text{O})\text{O}-\text{O}-\text{H}$, by the direct addi-

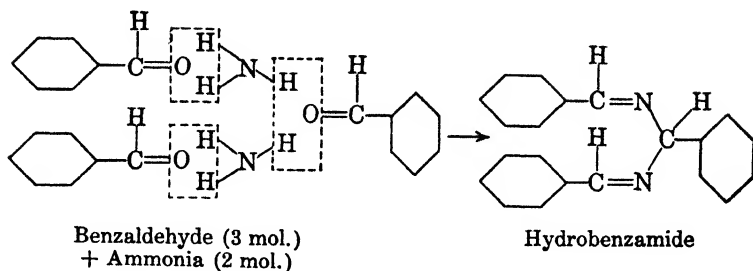
tion of a molecule of oxygen. The existence of the peroxide is demonstrated by the fact that benzaldehyde which has been exposed to oxygen can bring about the oxidation of substances which are unaffected by atmospheric oxygen, evidently by the liberation of part of the oxygen held in combination in the peroxide.

Gattermann's Reaction. Benzaldehyde may be prepared by one method which is unlike any that can be used for aliphatic aldehydes. This method involves the use of anhydrous aluminum chloride, and is similar to a Friedel-Crafts reaction. Carbon monoxide, hydrogen chloride gas, and benzene react in the presence of aluminum chloride and cuprous chloride. It is probable that the carbon monoxide and hydrogen chloride combine to form formyl chloride, which is very unstable but has recently been isolated at liquid air temperature. The formyl chloride may then react as follows in the presence of the catalysts.

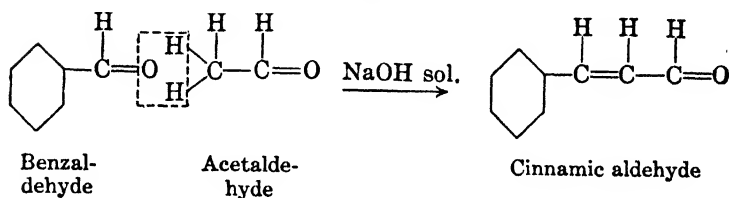


Condensation Reactions. Aside from condensations with hydroxylamine, phenylhydrazine, etc., benzaldehyde undergoes a variety of other condensations with different kinds of molecules including a condensation with itself. (Benzaldehyde does not polymerize reversibly as do many aldehydes.) Some of the more important condensations are indicated below.

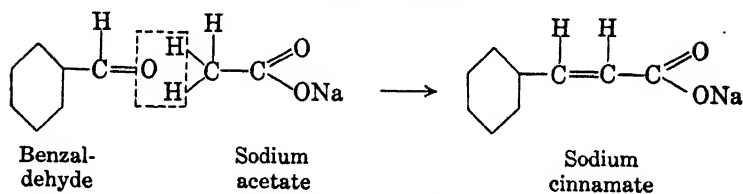
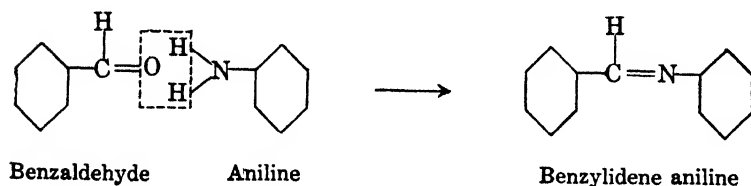




(II)

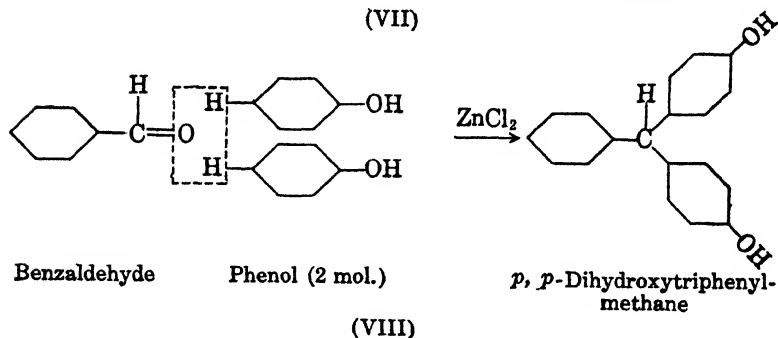
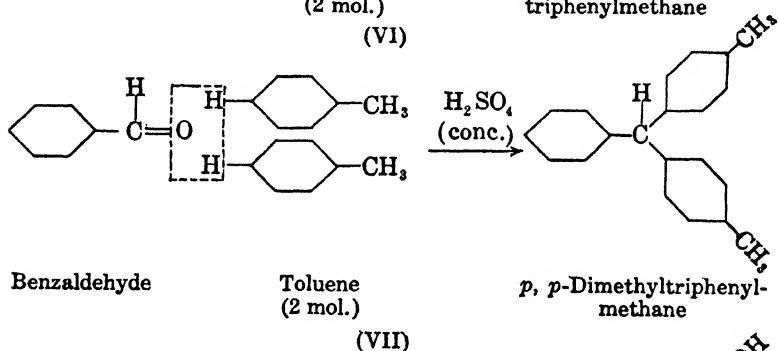
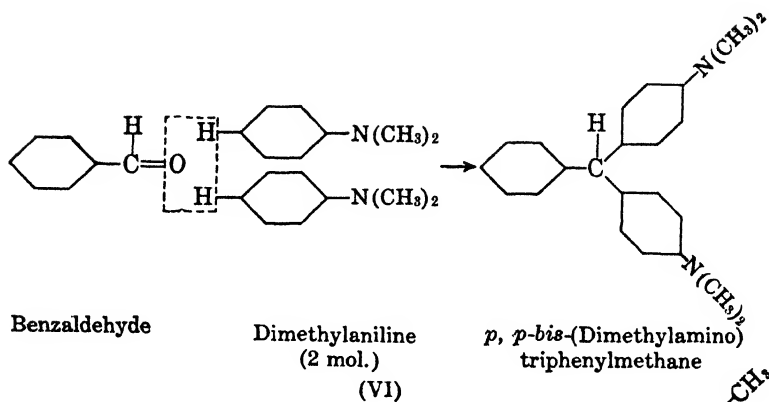


(III. Claisen's reaction)

(IV. Perkin's reaction²)

(V)

² Wm. H. Perkin, Senior (1838-1907), an Englishman, is famous for his discovery of "mauve," the first coal tar dye. This was discovered when he was 18 years of age, and before he was 20 years old he was manufacturing and marketing the dye. His work laid the foundation for the coal tar industry.



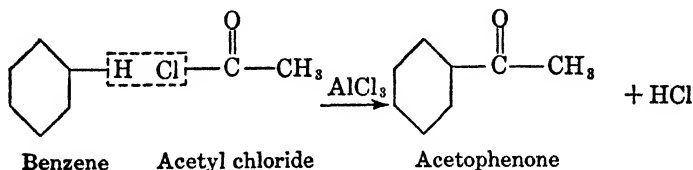
The similarity between these reactions will be noted. We might take considerable space to discuss these reactions and the products formed but a few statements must suffice at present; some of the products will be dealt with later. *Benzoin* (bĕn'zô-in) (I) is an example of a ketone alcohol or hydroxyketone. Like

levulose, which is also a hydroxyketone, benzoin reduces Fehling's solution, etc., and forms a hydrazone and a dihydrazone. It can be oxidized to a di-ketone, *benzil*, $C_6H_5COCOC_6H_5$. *Cinnamic aldehyde* (III) is, as the formula shows, an unsaturated aldehyde. It is the chief constituent of cinnamon oil, from which it may be obtained by treating the oil with sodium bisulfite, which forms a crystalline addition product. The similarity between the preparation of *p,p*-dimethyltriphenylmethane (VII) with the preparation of DDT from trichloroacetaldehyde and chlorobenzene (p. 431) should be noted.

Chlorination, Nitration. Benzaldehyde on treatment with chlorine at its boiling point yields *benzoyl chloride*, C_6H_5COCl . Substitution products in which the hydrogens of the nucleus are replaced by halogens are known but are not made directly. Benzaldehyde may be nitrated without oxidation, in which case the nitro group goes principally to the *meta* position. *o*-Nitrobenzaldehyde, which is made by indirect methods, can be readily converted by condensation with acetone into *indigo* which is an important dyestuff and will be discussed later.

Ketones

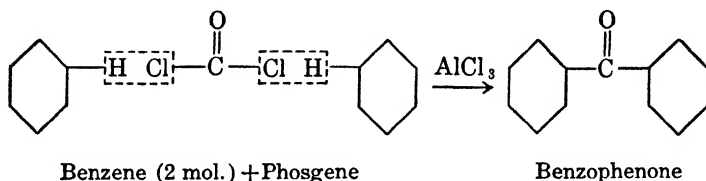
Acetophenone, $C_6H_5COCH_3$, is a typical example of a ketone in which one group attached to the carbonyl group is aliphatic and the other is aromatic. It can best be prepared by a Friedel-Crafts synthesis.



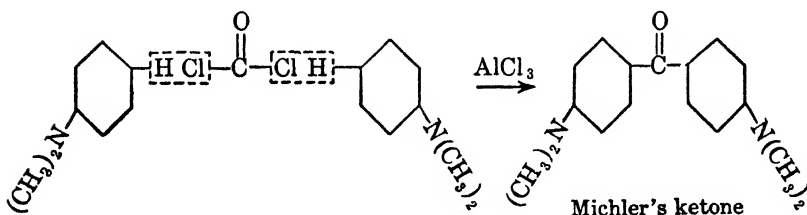
It differs in no outstanding way in chemical properties from the aliphatic ketones, as it enters into addition reactions, may be reduced to a secondary alcohol, etc. By oxidation, the methyl group is broken off and the carbon of the carbonyl group remains attached to the nucleus, forming benzoic acid. Acetophenone has been used as a hypnotic under the name of "hypnone" and

is now used in perfumes. Chloroacetophenone, $C_6H_5COCH_2Cl$, is a lacrymator and is frequently used as a "mob gas."

Benzophenone is a ketone with the structure $C_6H_5COC_6H_5$. It can be made in a way analogous to that given above for acetophenone, using benzoyl chloride, C_6H_5COCl , instead of acetyl chloride. It can also be made from phosgene (carbonyl chloride) by Friedel-Crafts reaction with benzene.

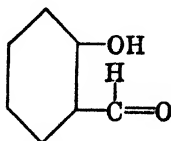


Michler's³ ketone is a derivative of benzophenone which is important as an intermediate in the manufacture of certain dyes. It is made by treatment of dimethylaniline with phosgene.



Complex Aldehydes, Etc.

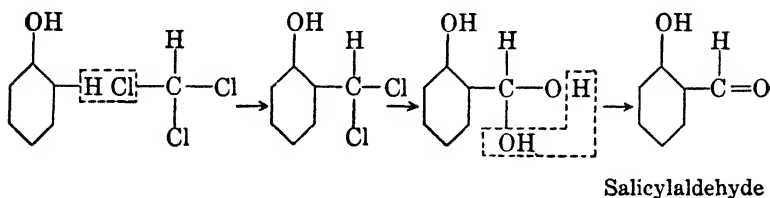
Salicylaldehyde is an example of a phenol-aldehyde, and has the formula



Salicylaldehyde

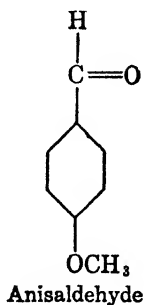
³ Wm. Michler (1846-1889) was Professor of Technical Chemistry in a polytechnic school in Rio de Janeiro, Brazil.

It may be obtained by oxidation of *saligenin*, the corresponding phenol alcohol, which is one of the products of hydrolysis of the glucoside *salicin*. Salicin occurs in the bark of the willow tree. Salicylaldehyde can be made synthetically from phenol, chloroform and alkali by reactions which are thought to take place as follows: ⁴



This reaction again illustrates the ease of substitution in the phenols.

Anisaldehyde is an ether-aldehyde of the formula:



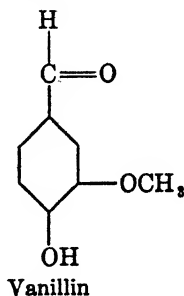
and is prepared from aniseed, from which it gets its name.

⁴ This synthesis is frequently called the Reimer-Tiemann reaction, and was discovered by Karl Reimer (1845-1915) and Ferdinand Tiemann (1848-1899) in the University of Berlin in 1876. Tiemann was an especially prolific worker in diversified fields. His work with the terpenes was especially important.

Aromatic Aldehydes

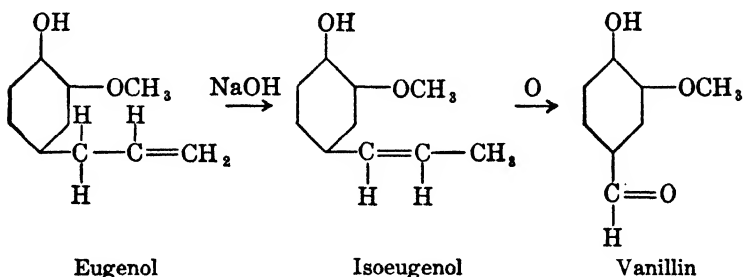
Compounds	M. P.	B. P.	Solubility grams in 100 ml.		
			Water	Alcohol	Ether
Benzaldehyde, $\text{C}_6\text{H}_5\text{CHO}$	-26°	179°	.33	inf.	inf.
<i>o</i> -Toluic aldehyde, $\text{C}_6\text{H}_4\text{CH}_3\text{-CHO}$	—	206°	v.sl.s.	inf.	inf.
Phenyl propionaldehyde, $\text{C}_6\text{H}_5(\text{CH}_2)_2\text{CHO}$	—	208°	ins.	17	—
Cumic aldehyde (<i>p</i>), $(\text{CH}_3)_2\text{-CH(4)C}_6\text{H}_4(1)\text{CHO}$	—	235°	ins.	sol.	sol.
<i>o</i> -Chlorobenzaldehyde, $\text{ClC}_6\text{H}_4\text{CHO}$	11°	213°	—	—	—
<i>m</i> -Chlorobenzaldehyde, $\text{ClC}_6\text{H}_4\text{CHO}$	17°	211°	—	—	—
<i>p</i> -Chlorobenzaldehyde, $\text{ClC}_6\text{H}_4\text{CHO}$	47°	213°	—	—	—
<i>o</i> -Nitrobenzaldehyde, $\text{NO}_2\text{C}_6\text{H}_4\text{CHO}$	46°	153° (23 mm.)	v.sl.s.	v.sol.	v.sol.
<i>m</i> -Nitrobenzaldehyde, $\text{NO}_2\text{C}_6\text{H}_4\text{CHO}$	58°	164° (23 mm.)	v.sl.s.	v.sol.	v.sol.
<i>p</i> -Nitrobenzaldehyde, $\text{NO}_2\text{C}_6\text{H}_4\text{CHO}$	107°	—	sl.s.hot	v.sol.	sol.
Anisaldehyde (<i>p</i>), $\text{CH}_3\text{O-C}_6\text{H}_4\text{CHO}$	0°	248°	sl.s.	inf.	inf.
Cinnamic aldehyde, $\text{C}_6\text{H}_5\text{CH=CHCHO}$	-7.5°	251°	v.sl.s.	inf.	inf.
Salicylaldehyde (<i>o</i>), $\text{C}_6\text{H}_4(\text{OH})\text{-CHO}$	-10°	196°	sl.s.	sol.	inf.

Vanillin is an ether-phenol-aldehyde of the formula:



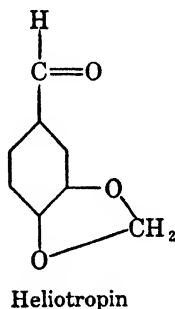
It is the characteristic constituent of the vanilla bean and is obtained in appreciable amounts by the oxidation of the waste sulfite liquors from the manufacture of cellulose pulp (p. 374). This is the principal source of vanillin. It is also made by oxida-

tion of *isoeugenol* which is obtained from *eugenol*, the characteristic constituent of cloves, and from *guaiacol* (p. 484) by reaction with chloroform similar to that indicated above for salicylaldehyde.

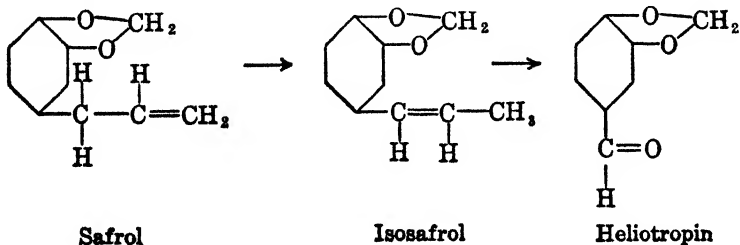


Vanillin is an important component of artificial flavors.

Heliotropin or piperonal is a cyclic acetal-aldehyde with the formula :



It has the odor of heliotrope and is used in perfumery. It is made from *safrol*, which is in the oil of sassafras, by reactions analogous to those by which vanillin is made from eugenol.



Aromatic Ketones and Alcohols

Compound and Formula	M. P.	B. P.	Solubility grams in 100 ml.		
			Water	Alcohol	Ether
Acetophenone, $C_6H_5COCH_3$..	20°		insol.	sol.	sol.
Butyl phenyl ketone, $C_6H_5COC_4H_9$	liquid	202°	insol.	v.sol.	v.sol.
Benzophenone, C_6H_5CO - C_6H_5	48.5°	306°	insol.	13.5(18°)	17.5(13°)
<i>p</i> -Chloroacetophenone, $ClC_6H_4COCH_3$	20°	230°	—	—	—
Benzyl alcohol, $C_6H_5CH_2OH$..		206°	4(17°)	inf.	inf.
<i>o</i> -Tolyl carbinol, $CH_3(2)$ - $C_6H_4(1)CH_2OH$	34°	223°	1(20°)	v.sol.	v.sol.
<i>m</i> -Tolyl carbinol, $CH_3(3)$ - $C_6H_4(1)CH_2OH$	liquid	217°	5	—	v.sol.
<i>p</i> -Tolyl carbinol, $CH_3(4)$ - $C_6H_4(1)CH_2OH$	59°	217°	sl.sol.cold	v.sol.	v.sol.
Benzyl carbinol, $C_6H_5CH_2$ - CH_2OH	—	219°	1.6(20°)	sol.	v.sol.
Hydrocinnamyl alcohol, $C_6H_5CH_2CH_2CH_2OH$	—	235°	—	—	—
Cinnamyl alcohol, C_6H_5CH : $CHCH_2OH$	33°	257.5°	mod. sol.	v.sol.	v.sol.

PROBLEMS

1. How much 0.1 N sulfuric acid would be necessary to neutralize the excess sodium hydroxide left after 0.5 gram of sodium hydroxide reacts with 0.5 gram of benzaldehyde?

2. Outline how oil of wintergreen (methyl salicylate) could be synthesized starting with benzene.

3. Would benzaldehyde be the sole product formed by heating calcium benzoate and calcium formate together? If not, what other compounds might be formed?

4. Suppose that an aromatic aldehyde when treated with a concentrated solution reacts with one-fourth of its weight of sodium hydroxide, what is the molecular weight of the aldehyde?

5. How many dihydroxyl compounds, derivatives of toluene, would be possible with the molecular formula, $C_7H_8O_2$?

6. Could benzaldehyde exist in an enol form analogous to the one thought to exist in the case of acetaldehyde?

7. Write the electronic formula for the peroxide of benzaldehyde.

8. From analogy with aliphatic compounds outline a method for the preparation of benzophenone which is not mentioned in the text.

9. Write the formula of the products formed when hydrocyanic acid, sodium bisulfite and phenylhydrazine react with benzaldehyde. Would any of these products exist in *syn* and *anti* forms?

CHAPTER XXX

AROMATIC CARBOXYLIC ACIDS

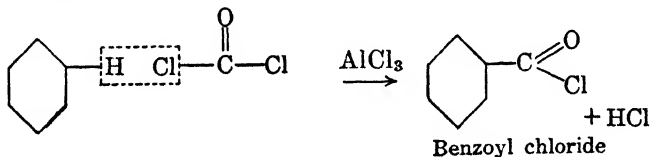
Monocarboxylic Acids

The fact that the homologs of benzene on oxidation yield carboxylic acids has already been noted. **Benzoic acid**, C_6H_5COOH , is the simplest aromatic acid and also an important one. It can be prepared in a variety of ways, the more important of which are indicated below.

1. Oxidation of toluene, benzyl alcohol, benzaldehyde, acetophenone, etc.; in fact, it can be obtained by the oxidation of practically any aromatic compound in which a phenyl group is attached to a carbon atom.

2. Hydrolysis of benzonitrile, C_6H_5CN , which can be made by the Sandmeyer reaction (p. 464) or by the action of potassium cyanide on benzene sulfonic acid (p. 445).

3. Hydrolysis of its esters or of its acid chloride; the latter can be made by the interaction of phosgene, aluminum chloride and benzene.



4. By Grignard reaction involving carbon dioxide.

Benzoic acid is, as we have indicated, the oxidation product of a large number of compounds, and is itself very difficultly oxidized. In animal organisms it is formed by the oxidation of various aromatic compounds and is not further oxidized, but is condensed with glycine to form *hippuric acid*, $C_6H_5CONHCH_2COOH$, which is excreted in the urine. It may be made technically by oxidation of toluene or by elimination of carbon dioxide from phthalic acid (p. 516) in the vapor state through the agency of steam and contact catalysts. When made from toluene it may be made by direct oxidation or by chlorination followed by hydrolysis of the benzotrichloride, $C_6H_5CCl_3$, which is formed.

Benzoic acid is a crystalline substance with melting point 121° and boiling point 250° . It is found in nature in many sources notably in cranberries. It has appreciable vapor pressure at the boiling point of water and so may be distilled with steam; it also sublimes readily when heated. In acid strength benzoic acid lies intermediate between acetic and formic acids. It has the properties common to acids as it forms salts, an anhydride, acid chloride, esters, amides. By heating with lime it breaks up analogous to sodium acetate (p. 140), giving benzene and calcium carbonate. It is used most in the form of its sodium salt as a preservative for fruit juices, etc. The benzyl ester, benzyl benzoate, is a very effective insecticide for chiggers.

Benzoyl (běn'z6-ĭl) **chloride**, C_6H_5COCl , can be made from benzoic acid by the action of phosphorus pentachloride, but is made technically by chlorination of benzaldehyde. Contrary to what might be expected it is less reactive with water and alcohols than acetyl chloride.¹ In contact with water it undergoes hydrolysis, and also reacts with alcohols, phenols, ammonia, primary and secondary amines, forming hydrogen chloride in each case, in addition to the ester or amide. The reactivity of benzoyl chloride increases in the presence of alkali so it is used along with alkali to form benzoyl derivatives of alcohols, phenols, etc.² The

¹ As pointed out previously (p. 158) the general relationship between the strength of acids and the reactivity of their anhydrides does not hold invariably. Anhydrides of stronger acids are in general more reactive, but it is unsafe to rely on the generalization when comparing substances of quite different structure or composition. In comparing aromatic and aliphatic anhydrides, the generalization may not hold while the comparative behavior of similar members of either group may be predicted with more certainty. There are evidently factors other than the strengths of the acids concerned, which affect the reactivity of their anhydrides.

² The reaction of benzoyl chloride in alkaline solution is known as the Schotten-Baumann reaction. Carl Schotten (1853-1910) was Professor in the University of Berlin. His principal work was in the field of physiological chemistry. Eugen Baumann (1846-1896) was Professor of Chemistry in the Medical faculty of the University of Freiburg. He was responsible for the synthesis of several naturally occurring substances of physiological importance and was one of the leading physiological chemists of his time.

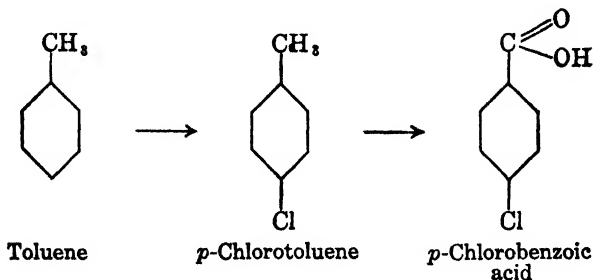
benzoylated products are often more easily crystallized and purified than the original hydroxyl compounds, and from them, if desired, the original hydroxyl compound may be recovered by hydrolysis.

Benzamide, $C_6H_5CONH_2$, is formed by ammonolysis of benzoyl chloride. Its base-forming property is practically nil but it has slight acid properties, and dissolves in alkalis.

Benzonitrile, C_6H_5CN , is formed by the action of phosphorus pentoxide on benzamide and also may be prepared from a diazonium salt by Sandmeyer's reaction. On hydrolysis it yields ammonium benzoate in which respect it behaves like the other nitriles.

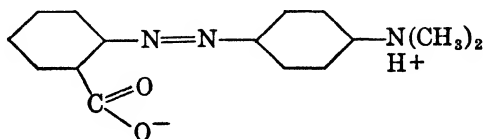
Dibenzoyl peroxide, $(C_6H_5COO)_2$, is prepared by stirring benzoyl chloride at 0° with a dilute solution of sodium peroxide. It is used extensively to bleach flour.

Substituted benzoic acids are formed by treatment of benzoic acid with chlorine, bromine, nitric acid or sulfuric acids. In each case the principal product first formed is the *meta* substitution product. With nitric acid there are formed appreciable amounts of all three kinds of nitrobenzoic acids. If toluene is treated with any reagent which brings about substitution, the *ortho* and *para* substitution products are formed as has already been indicated. The oxidation of these substituted toluenes constitutes a general method for the preparation of *ortho* and *para* substituted benzoic acids. This is illustrated by a single case below.



Anthranilic acid or *o*-aminobenzoic acid, $C_6H_4(NH_2)COOH$, is of some importance because its methyl ester is a constituent of

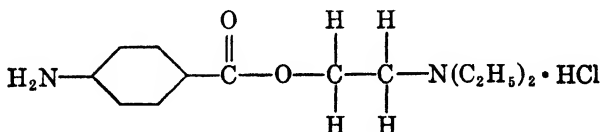
oil of orange blossoms and oil of jasmine, and is used in perfumery. Anthranilic acid is also used in the manufacture of certain azo dyes. It is both an acid and a base-forming substance and thus exists in the form of an inner salt. It forms an inner diazonium salt like that formed from sulfanilic acid, and this salt condenses with dimethylaniline to form *methyl red* with the structure indicated.



Methyl red

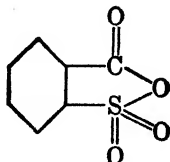
This compound is a very useful indicator in acid-alkali titrations as it gives a sharp end point. It is sensitive to weak bases and hence is often used when ammonia is being titrated.

Novocaine is a very valuable local anesthetic which is related to *p*-aminobenzoic acid, as shown in its formula.

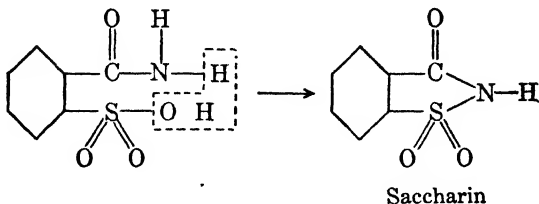


Novocaine

There are three *sulfobenzoic acids*, $C_6H_4(SO_3H)COOH$, only one of which (*meta*) can readily be made by treatment of benzoic acid with sulfuric acid. The others may be made indirectly like the *ortho* and *para* chlorobenzoic acids mentioned above. The *ortho* compound forms an inner anhydride of the structure (see footnote p. 485):

*o*-Sulfobenzoic anhydride

The amide of *o*-sulfobenzoic acid may be made to lose a molecule of water, and form an imide as indicated.



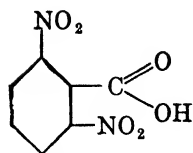
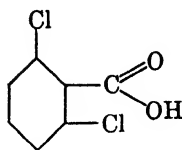
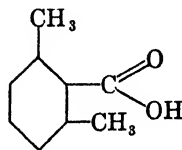
This imide is what is known as **saccharin**,³ and is about 500 times as sweet as cane sugar. It does not serve as a food but does furnish diabetics and others who cannot tolerate sugars a substance with a sweet taste. Except in very dilute solutions it tastes bitter.

Toluic acids or methyl benzoic acids exist in the three isomeric forms. They can be made by the careful oxidation of the corresponding xylenes, or by other of the general methods.

Steric Hindrance. As stated above, benzoic acid is able to react with the alcohols to form esters. These reactions are slow, like other esterifications, and a catalyst is used to hasten the process. The alcoholic solution of the acid may be saturated with dry hydrogen chloride and after some time an equilibrium is reached. It was noted by Victor Meyer⁴ that especially in the case of the di-*ortho* substituted benzoic acids such as the following:

³ This compound was first prepared under the direction of Ira Remsen (1846-1927), an outstanding pioneer organic chemist of America. He was Professor of Chemistry and later President of Johns Hopkins University. He was the founder and editor of the "American Chemical Journal" and the author of a series of textbooks.

⁴ Victor Meyer (1848-1897) was Professor of Chemistry at Göttingen and Heidelberg. He is known principally for his work on steric hindrance and for his vapor density method of molecular weight determination, although his researches were by no means limited to these lines of work.

2, 6-Dinitrobenzoic
acid2, 6-Dichlorobenzoic
acid2, 6-Dimethyl-
benzoic acid.

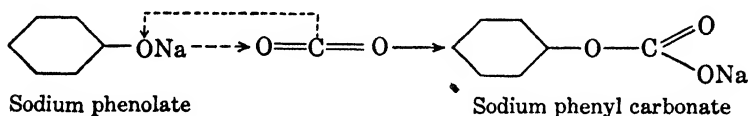
The formation of esters does not take place, and even in case of the *ortho* monosubstituted acids the rate of esterification is markedly slower than that of benzoic acid. This effect might be attributed to the modification of the properties of the carboxyl group through the chemical influence of the substituted groups. The substituted groups are known to influence, among other properties, the tendency toward ionization. That the chemical influence of the substituted groups is not wholly responsible for the difficulty of esterification is shown by the fact that the hindrance caused by groups is in many cases dependent on their weight rather than upon their chemical character. Thus the methyl and fluorine radicals with about the same weight seem to act very much alike, in spite of their very great chemical difference.

Esters of the above mentioned acids can be prepared but not by the simple method. The effect of the groups in preventing the esterification is thought to be due to spacial interference; that is, the presence of the nearby groups prevents the alcohol molecules from coming in contact and reacting with the carboxyl groups. The same hindrance is also observed when one attempts to hydrolyze the esters of the above acids. The surrounding groups presumably prevent the reaction with water. This phenomenon of spacial interference is known as *steric hindrance*, and while these cases constitute classic examples of this type of behavior, we have already noted other examples. Probably steric effects are rather common even among simpler compounds.

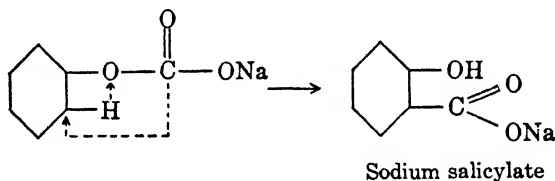
The fact that the above acids retain their acid properties (give rise to hydrogen ions) but lose their ability to form esters indicates plainly that in esterification reactions the acid and alcohol

molecules must collide and therefore the reactions are of the type which take place between molecules.

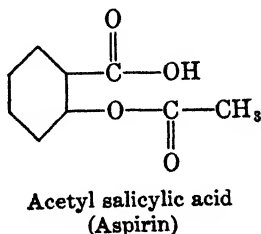
Salicylic acid, *o*-hydroxybenzoic acid, is the most important phenol-acid. It may be made by several different methods which are applications of reactions already discussed. It is manufactured by a reaction analogous to that which resorcinol (p. 485) undergoes. When sodium phenolate is heated with carbon dioxide an addition reaction takes place which is analogous to the combination of sodium hydroxide and carbon dioxide.



At about 125° this compound undergoes a rearrangement in which the —COONa group exchanges positions with an *ortho* hydrogen atom, giving sodium salicylate (säl'-i-sil-ät).



If heated to a higher temperature the entering group takes the *para* position. Salicylic acid itself is used in medicine, but its derivatives are more important for this purpose. The salicylic acid derivatives are similar in physiological action. The most important derivative is "aspirin" which is the acetyl derivative of salicylic acid (ester of the phenol).



It is made by heating salicylic acid and acetic anhydride. The methyl ester of salicylic acid is the chief component of *oil of wintergreen* and is made in large quantities for use in perfumery and in flavoring confectionery. It is used also in the manufacture of certain azo dyes. The yearly consumption of salicylic acid and its derivatives in America runs into thousands of tons per year.

In the following table is given the ionization constants and percentage ionizations of various substituted benzoic acids. The effects of the groups in different positions should be noted.

Acid	Ionization constants	Per cent ionized in .1 N solution
Benzoic000066	2.6
<i>o</i> -Chlorobenzoic00132	10.8
<i>m</i> -Chlorobenzoic000155	3.85
<i>p</i> -Chlorobenzoic000093	3.0
<i>o</i> -Bromobenzoic00145	11.3
<i>o</i> -Hydroxybenzoic (Salicylic)00105	9.6
<i>o</i> -Nitrobenzoic00615	21.9
<i>m</i> -Nitrobenzoic000345	5.8
<i>p</i> -Nitrobenzoic000401	6.1
<i>o</i> -Methylbenzoic (<i>o</i> -Toluic)000125	3.4
<i>m</i> -Methylbenzoic (<i>m</i> -Toluic)000052	2.25
<i>p</i> -Methylbenzoic (<i>p</i> -Toluic)000045	2.10

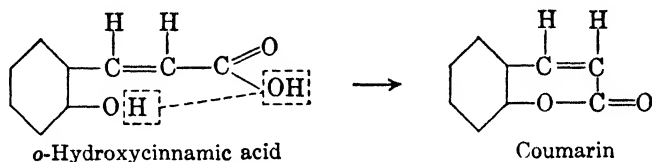
It will be noted that *o*-toluic acid is stronger than benzoic acid. This is an exception to the general rule that replacement of a hydrogen atom by methyl decreases acidity.

Phenylacetic acid, $C_6H_5CH_2COOH$, is an example of an aromatic acid in which the carboxyl group is not attached to the nucleus. It is slightly stronger than acetic acid but weaker than benzoic. Its general character resembles the higher fatty acids though it has the benzene nucleus and reacts accordingly. It can be oxidized to benzoic acid.

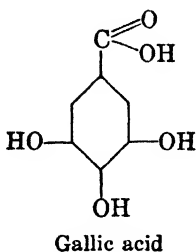
Cinnamic acid, $C_6H_5CH=CHCOOH$, is the most important member of the class of unsaturated aromatic acids. It sometimes occurs free, and exists in the form of benzyl esters in certain balsams. Ordinary cinnamic acid is thought to be the *trans* isomer. The *cis* isomer is also known and exists in three forms, that is, it crystallizes in three different ways and gives substances

with melting points 68° , 58° and 42° . These substances can be converted into one another by melting and inoculating the melt with the crystal of the desired kind. The difference between the crystalline form is due not to a difference in the structure of the molecules which make up the crystals but to a difference in the arrangements of molecules in the crystals. This phenomenon is called *polymorphism*. Ordinary cinnamic acid melts at 133° .

o-Hydroxycinnamic acid is of interest because of the inner ester which it forms. This ester is known as *coumarin* (kōō'mā-rīn) and is a constituent of tonka beans. It is used in perfumery, also as a substitute for, or adulterant of vanilla, and for flavoring tobacco. It is made synthetically.



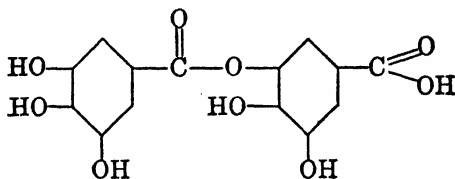
Gallic acid is one of six theoretically possible trihydroxybenzoic acids and has the formula



It occurs free in gallnuts, tea, and in other vegetable sources. When heated it decomposes into carbon dioxide and pyrogallol and this reaction has been employed for the manufacture of pyrogallol. The ready elimination of the carboxyl group by heating is characteristic of other polyphenolic acids. Gallic acid reduces Fehling's solution like other polyhydroxy phenols. It has been employed as a mordant in dyeing.

Tannic Acids. This term applies to a large number of acid substances which are of vegetable origin, but whose structures are not fully known. The substances which are classed under this heading have the following characteristics. They form colloidal solutions, are weak acids, reduce Fehling's solution and ammoniacal silver solutions readily, produce a dark coloration with ferric chloride, have an astringent taste, and are able to precipitate proteins from their solutions. Any substance with these characteristics may be termed a *tannin* or *tannic acid*. The substances with these characteristics are common constituents of the bark of quebracho, oak, hemlock and sumac and other trees. They also occur in gallnuts, the warty masses which grow on trees as a result of insects puncturing the bark. Though these are the commercial sources of tannins or tannic acids, similar substances are very widely distributed in nature and are frequently encountered in the extracts of plants. The complex tannins can be hydrolyzed and in some cases gallic acid is one of the products; in other cases acids of similar character are formed.

Digallic acid is an intermediate substance formed in the hydrolysis of some complex tannic acids. It is derived from gallic acid by the condensation of two molecules with the elimination of water. Its structure is represented below.



Digallic acid

It is an ester and can be hydrolyzed to form gallic acid.

The tannic acid from Chinese gallnuts produces gallic acid and glucose on complete hydrolysis, in the proportion of ten molecules of gallic acid to one molecule of glucose. Emil Fischer synthesized the pentadigalloyl derivative of glucose, which has the same relation to digallic acid as the penta-acetyl derivative of glucose has to acetic acid. This synthetic substance is similar in

properties and yields the same products on hydrolysis as the tannic acid from Chinese gallnuts, and may be the same substance. This tannin, since it yields glucose on hydrolysis, may be classed as a glucoside.

Uses of Tannic Acids. The tannic acids in the form of crude extracts are used for tanning hides to produce leather. The essential thing about a tanning agent is that it combines with the proteins of the hide to form insoluble and unreactive material. Many substances which will precipitate proteins readily produce effects similar to tanning. Salts or oxides of heavy metals may be used to bring about such a change. The production of marketable leather which is necessarily pliable, tough, durable, etc., can be accomplished only by proper preparation of the hide, by careful control of the conditions of tanning and by the use of the proper tanning materials. Tanning is often accomplished not by the use of pure compounds of known composition but by the use of crude extracts of barks in which the tanning agent is present. Synthetic organic tanning materials are also used which are made from different phenols and formaldehyde. The extract of gallnuts is too expensive to be used for tanning, but may be used as a source of pyrogallol, as a mordant in dyeing, and in the manufacture of writing inks. Chrome tanning which involves the use of chromium salts has grown to be of great importance for the production of light leathers.⁵

Blue-black writing inks may be made by mixing an extract of gallnuts, ferrous sulfate, a blue dye, gum arabic and a trace of an acid. The blue dye renders the ink visible while it is used, the gum arabic makes it flow smoothly from the pen and prevents it spreading throughout the paper, the ferrous sulfate and tannic acid remain in solution together as long as the ferrous salt is not oxidized, but after exposure to the air the ferrous salt is oxidized to the ferric salt and reacts with the tannic acid to form an insoluble black precipitate. The ink is made slightly acid so that it will not oxidize before it is used. Writing inks are made in

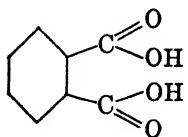
⁵ For more information on tanning, the student is referred to J. A. Wilson, "The Chemistry of Leather Manufacture," 2 vols. (1929), Chemical Catalog Co.

which there is no tannic acid, but in which all of the color is contributed by organic dyes. There are a very large number of different types of ink, both for writing and printing purposes, and the interested student is referred to other sources of information.⁶ (It may be pointed out that books are not always ideal sources of information in regard to manufacturing processes, simply because processes are constantly changing, and there are almost invariably some secrets which the manufacturers take pains not to advertise. The practices in different factories are by no means uniform.)

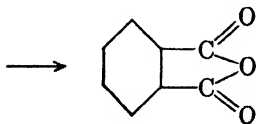
Acids with More than One Carboxyl Group

Acids derived from benzene are known, in which there are one, two, three, four, five, or six carboxyl groups substituted for hydrogen atoms. Of the polycarboxylic acids only the dicarboxylic acids are of importance.

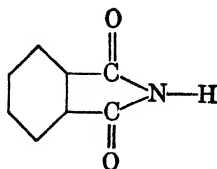
Phthalic acid, benzene-*o*-dicarboxylic acid, is much the most important dicarboxylic acid. It can be formed by the oxidation of *o*-dimethylbenzene (*o*-xylene) or any other hydrocarbon in which two side chains are attached to the benzene nucleus in the *ortho* position. It is manufactured by oxidizing both xylene and naphthalene (p. 540) with oxygen in the presence of oxides of vanadium. When heated rapidly phthalic acid melts at 213°, but if the heating is carried on more gradually it decomposes into water and phthalic anhydride which melts at 131°. This behavior is similar to that of succinic acid to which phthalic acid bears a resemblance in structure (p. 422).



Phthalic acid



Phthalic anhydride

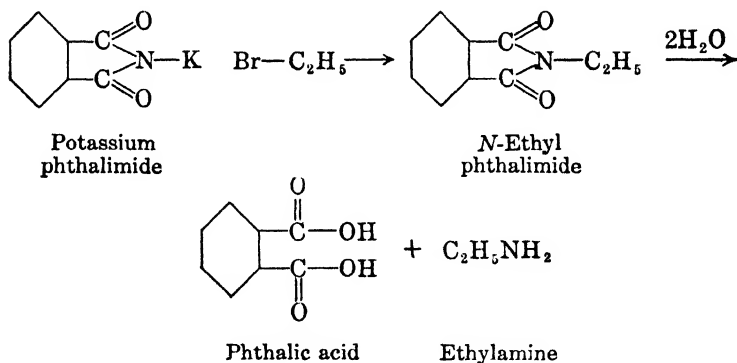


Phthalimide

⁶ For a general discussion and bibliography on such topics see Thorpe, "Dictionary of Applied Chemistry," Longmans, Green & Co., also see references to current articles and recent books in the Industrial Arts Index (p. 635).

Phthalic acid, due to the reinforcement of the second carboxyl group, is a much stronger acid than benzoic acid. It forms many different types of derivatives such as salts, esters, amides, etc. The dimethyl ester of phthalic acid is used as a mosquito repellent.

Phthalimide shows a resemblance to succinimide in that the hydrogen attached to the nitrogen ionizes slightly due to the influence of the neighboring carbonyl groups. When treated with alcoholic potassium hydroxide solution it forms the potassium derivative. The potassium derivative may be made to react with alkyl iodides and more complex halides, and the products formed may be hydrolyzed to form simple or substituted primary amines, depending on the original halides used. The reaction which is known as *Gabriel's⁷ synthesis* is illustrated by a simple case below.

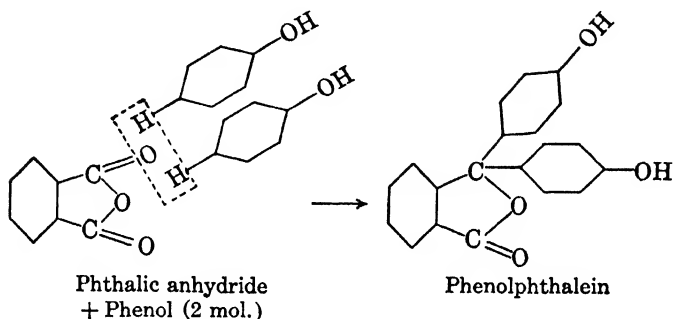


Potassium acid phthalate, $\text{C}_6\text{H}_4\text{COOHCOOK}$, is an excellent reagent for the standardization of alkali solutions, since it can be obtained very pure and may be handled safely in the air without taking up water. It is also used in preparing buffer solutions for hydrogen ion determinations.

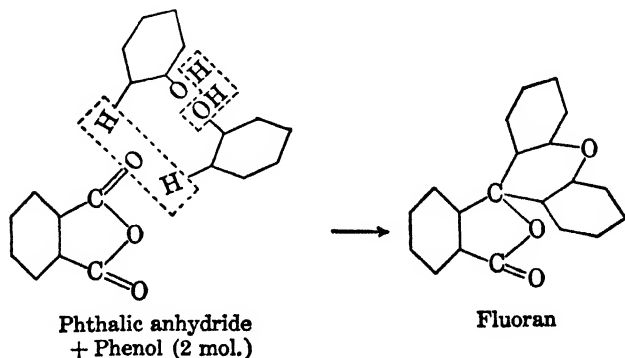
Phthalic anhydride is the most important derivative of phthalic acid. Its use in the manufacture of "glyptal" resins has been mentioned. It reacts rather slowly with water to form

⁷ S. Gabriel (1851-1924), Professor of Chemistry in the University of Berlin.

phthalic acid, but it hydrolyzes readily in the presence of alkalis. The most important reaction of phthalic anhydride is with phenols in the presence of a dehydrating agent such as sulfuric acid. The substances formed by this type of reaction are *phthaleins*. When phenol itself is used the simplest of the phthaleins is formed, which is the familiar indicator and laxative *phenolphthalein* (fē'nōl-thāl'ē-īn). In this condensation, substitution takes place in the *para* position on the phenol molecules.



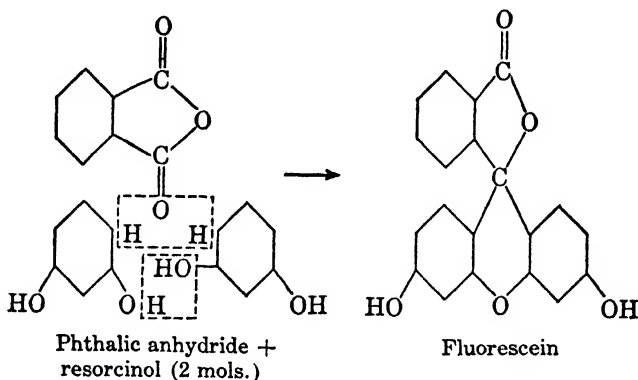
At the same time some substitution takes place in the *ortho* position in which case another reaction follows the first condensation as indicated below.



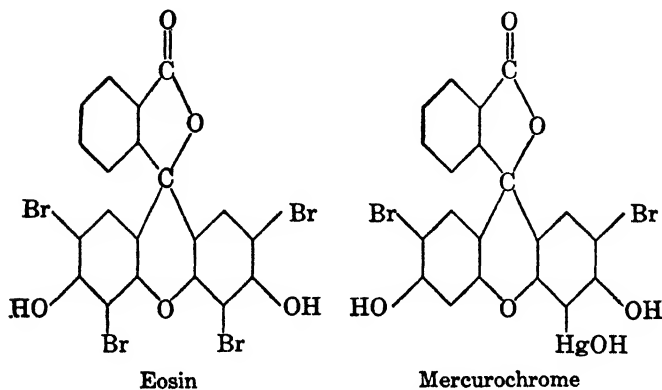
It will be noted that a six-membered ring is formed by this second condensation. This latter reaction is not cited because of its importance as an individual reaction but because it illustrates how more complex derivatives may be formed. Phenolphthalein

with the structure given above is colorless like most of the compounds which we have so far studied. The color produced when phenolphthalein is treated with alkali will be discussed later.

Fluorescein is a compound which is derived from phthalic anhydride as indicated below. Its dilute solutions show remarkable fluorescence.



Eosin, a dye which is used in red inks, and *mercurochrome*, an antiseptic, are derivatives of fluorescein as is apparent from their formulas.



m-Phthalic acid (isophthalic acid) and *p*-phthalic acid (terephthalic acid) may be prepared by oxidation of various *meta* and *para* compounds. These acids, however, are not of sufficient im-

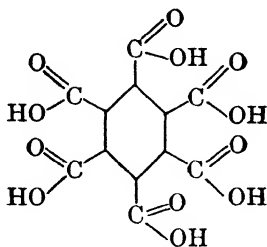
portance to merit detailed discussion. Neither the *meta* nor the *para* di-acid forms inner anhydrides as does phthalic acid.

Aromatic Acids

Compound	M. P.	B. P.	Sol. H ₂ O	Sol. Alc.	Sol. ether
Benzoic acid, C ₆ H ₅ COOH	121°	250°	.29 (20°)	47 (15°)	31 (20°)
<i>o</i> -Propylbenzoic acid, C ₆ H ₄ (C ₃ H ₇)COOH ..	58°	272°	sol.	v.sol.	v.sol.
Cumic acid, <i>p</i> -Iso- propylbenzoic acid, C ₆ H ₄ (C ₃ H ₇)COOH .	117°	subl.	v.sl.s. cold	sol.	v.sol.
Phenylacetic acid, C ₆ H ₅ CH ₂ COOH	76.5°	265.5°	v.sol. hot	v.sol.	v.sol.
Hydrocinnamic acid, C ₆ H ₅ CH ₂ CH ₂ COOH .	48.7°	280°	.59 (20°)	v.sol.	sol.
Cinnamic acid, C ₆ H ₅ - CH:CHCOOH	133°	300°	.05 (25°)	23 (20°)	v.sol.
<i>o</i> -Nitrobenzoic acid, C ₆ H ₄ (NO ₂)COOH .	147.7°		.68 (20°)	28 (10°)	21.6 (11°)
<i>m</i> -Nitrobenzoic acid, C ₆ H ₄ (NO ₂)COOH .	141°		.31 (20°)	33 (10°)	25.1 (11°)
<i>p</i> -Nitrobenzoic acid, C ₆ H ₄ (NO ₂)COOH .	242°		.04 (20°)	.09 (10°)	2.2 (11°)
Anthranilic acid, NH ₂ - (2)C ₆ H ₄ (1)COOH..	145°	dec.	.34 (14°)	10.7 (9.6°)	16 (7°)
<i>o</i> -Phthalic acid, C ₆ H ₄ (COOH) ₂	213°		.54 (14°)	v.sol.	.69 (15°)
Salicylic acid, HO(2)- C ₆ H ₄ (1)COOH	159°	subl.200	.27 (20°)	46.85 (25°)	47.68 (25°)
Anisic acid, CH ₃ O- (4)C ₆ H ₄ (1)COOH	185°	280°	.04 (18°)	v.sol.	sol.
Isophthalic acid, COOH(3)C ₆ H ₄ (1)- COOH	abt. 300°	subl.	.013 (2.5°)	mod. sol.	
Terephthalic acid, COOH(4)C ₆ H ₄ (1)- COOH	subl.	subl.	.0016	v.sl.s.	insol.
Mandelic acid, C ₆ H ₅ CHOHCOOH..	118°	dec.	16 (20°)	sol.	sol.

Mellitic acid, C₆(COOH)₆, is found in lignite and peat beds in the form of an aluminum salt, known as *honey stone* or *mellite*. The acid can be made by oxidation of hexamethylbenzene, and even by the direct oxidation of graphite or charcoal with potassium permanganate or nitric acid. Its production by the latter method is interesting because X-ray evidence indicates that the structure of graphite crystals involves symmetrical arrangement

of carbon atoms in groups of six resembling in form and dimensions the structure of benzene molecules.



Mellitic acid

Derivatives of Aromatic Acids

Compound and Formula	M. P.	B. P.	Sol. H ₂ O	Sol. Alc.	Sol. ether
Benzoyl chloride, $\text{C}_6\text{H}_5\text{COCl}$	-1°	198°	dec.	dec.	inf.
Benzoic anhydride, $(\text{C}_6\text{H}_5\text{CO})_2\text{O}$	42°	360°	insol.	sol.	sol.
Benzoyl peroxide, $(\text{C}_6\text{H}_5\text{CO})_2\text{O}_2$	103°	deflagrates	sl.sol.	sol.	v.sol.
Benzamide, $\text{C}_6\text{H}_5\text{CONH}_2$	130°	288°	1.35 (25°)	17 (25°)	v.sol.
Benzonitrile, $\text{C}_6\text{H}_5\text{CN}$..	-13.1°	191°	1 (100°)	inf.	inf.
o-Phthalyl chloride, $\text{C}_6\text{H}_4 \left\{ \begin{array}{l} (1) \text{COCl} \\ (2) \text{COCl} \end{array} \right. \dots\dots$	0°	281.5°	dec.	dec.	sol.
Phthalic anhydride, $\text{C}_6\text{H}_4 \left\{ \begin{array}{l} (1) \text{CO} \\ (2) \text{CO} \end{array} \right\} \text{O} \dots\dots$	130.8°	284°	v.sl.sol.	sol.	sl.sol.
Phthalimide, $\text{C}_6\text{H}_4 \left\{ \begin{array}{l} (1) \text{CO} \\ (2) \text{CO} \end{array} \right\} \text{NH} \dots\dots$	238°	subl.	v.sl.sol.	v.sl.sol.	sl.sol.
Phthalic diamide, $\text{C}_6\text{H}_4 \left\{ \begin{array}{l} (1) \text{COHN}_2 \\ (2) \text{CONH}_2 \end{array} \right. \dots\dots$	220°				
Benzotrichloride, $\text{C}_6\text{H}_5\text{CCl}_3$	-22.5°	213°	dec.		
Benzamidine, $\text{C}_6\text{H}_5\text{C} \begin{array}{l} \text{//} \text{NH} \\ \backslash \text{NH}_2 \end{array} \dots\dots$	$75-80^\circ$		mod. sol.	v.sol.	sl.sol.
Benzyl cyanide, $\text{C}_6\text{H}_5\text{CH}_2\text{CN}$	-24.6°	232°	insol.	inf.	inf.

Meta and Para Rings. In connection with the well known fact that *ortho* rings (5 membered) form readily as in anhydrides, imides, etc., it is interesting to note that rings connecting the *meta* positions and the *para* positions are also possible when a relatively large number of atoms are involved. Thus *meta* rings with 13 or more members have been prepared and *para* rings with 16 or more members.

PROBLEMS

1. What is the formula of the compound obtained by heating phenylacetic acid with soda lime?
2. Work out the formulas for the six trihydroxybenzoic acids.
3. Outline a method by which anthranilic acid might be made.
4. What difference would you expect in the "solubility" of benzoic acid in dilute alkaline and dilute acid solutions? Why?
5. How can *o*-sulfobenzoic acid be prepared?
6. How many acids, derivatives of toluene, would be possible with the formula $C_7H_6(COOH)_2$?
7. Would you expect cranberries to be easily susceptible to bacterial decay? Why?
8. In the crystals of a simple substance like common salt, the units out of which the crystals are built are believed to be the sodium and chlorine atoms or ions; the molecules as such are not present. Do the molecules of organic compounds lose their identity in a similar way in crystals? What is the evidence?
9. Would you expect *m*- and *p*-sulfobenzoic acids to form inner anhydrides and imides? Why? Actually they do not.
10. It is only by extraction for some little time with hot water that appreciable amounts of tannins are extracted from tea leaves. May this fact be related to the colloidal character of the tannin?
11. Would it be easy to stop, with the introduction of four bromine atoms into fluorescein? Why?
12. Could the idea of steric hindrance in any way explain the difficulty with which proteins are hydrolyzed?

13. Dihydro-, tetrahydro-, and hexahydrophthalic acids are known. Write a formula representing each of the three types. The last is a derivative of cyclohexane.

14. How can you explain the fact that benzyl cyanide reacts with sodium while benzonitrile does not?

15. A test for methyl alcohol is based upon the formation of oil of wintergreen which has a characteristic odor. How might the test be carried out on an unknown alcohol?

16. A hydrocarbon to be studied later, known as naphthalene, when oxidized produces phthalic acid. From this fact alone what could safely be inferred as to the structure of naphthalene?

17. When carboxylic acids are heated with lime, hydrogen (positive) takes the place of the carboxyl group. On the basis of the pull on electrons ordinarily exerted by oxygen, would you expect the carboxyl group to be positive or negative with respect to the carbon of the benzene nucleus? Does it seem safe to interpret high temperature reactions on the basis of expected electron displacements?

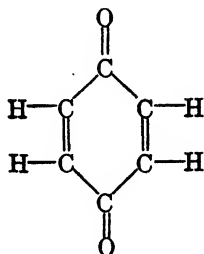
CHAPTER XXXI

QUINONES

When quinol, *p*-aminophenol, and many other *para* derivatives are partially oxidized, there is produced a substance with the molecular formula $C_6H_4O_2$, known as **quinone**. This same substance is also produced and is commonly prepared by the oxidation of aniline with dichromate and sulfuric acid. However, in any case, other substances are formed at the same time and if the conditions are not controlled, the quinone itself is oxidized.

Quinone is a yellow crystalline substance melting at 116° and has a characteristic sharp odor. As might be expected from its distinct odor it is readily volatile with steam. It is unstable and turns brown on exposure to air. The color of quinone is a characteristic and important property, as quinones and quinone derivatives are in general colored substances, and make up some of the most important dyes.

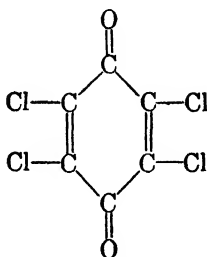
Structure. Quinone reacts with hydroxylamine to form a monooxime and a dioxime. This fact indicates the presence of two carbonyl groups. Taking this into consideration and also its preparation from *para* compounds, the only structure which appears to be reasonable is



Quinone
(*p*-Benzoquinone)

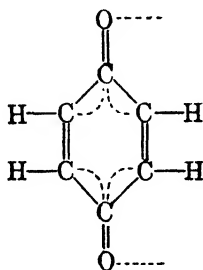
This structure seems to be justified by the fact that in chloroform solution quinone has been found to show unsaturated properties, and adds on two or four atoms of bromine.

It must be admitted, however, that quinone does not always act as would be expected of a substance with the above structure. For example, it forms a *substitution* rather than an addition product when treated with chlorine. The substitution product is *tetrachloroquinone*.



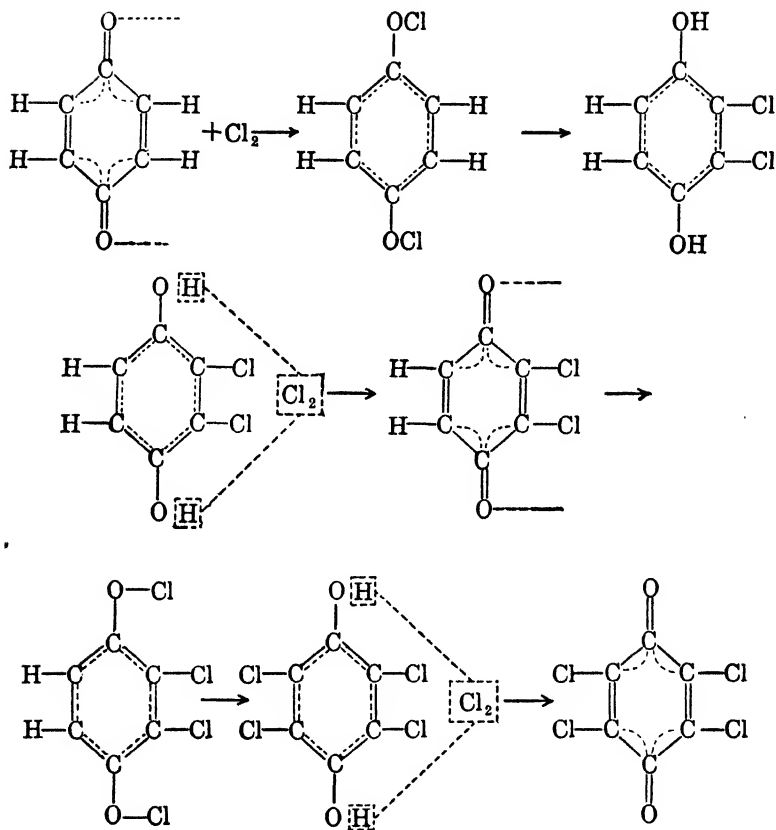
Tetrachloroquinone (chloranil)

This behavior, however, may be explained on the basis of partial valences in a conjugated system. Though the formula for quinone does not possess the conjugated system which is characteristic of benzene, it does present a conjugation of a different type (p. 292) and its structure may be pictured as follows:



Quinone
(Partial valence formula)

According to this structure the points at which addition would be expected to take place most readily are on the oxygen atoms. This in fact may happen followed by a rearrangement as indicated.

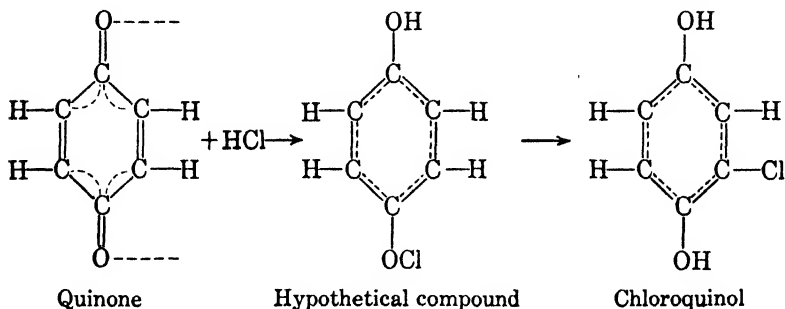


Tetrachloroquinone

Formation of Tetrachloroquinone (hypothetical mechanism)

Though the reaction may not take place exactly in this manner, there are none of the hypothetical steps which seem unreasonable. The rearrangement after addition of chlorine to the oxygen is analogous to the similar rearrangement which is known to take place when a halogen is attached to nitrogen in acetchloroanilide (p. 450). In the next step the chlorine acts as an oxidizing agent and the oxidation is analogous to the oxidation of quinol to quinone.

Quinone also enters an addition reaction with hydrogen chloride which falls in line with the above interpretation, and may be pictured as taking place in the following way.



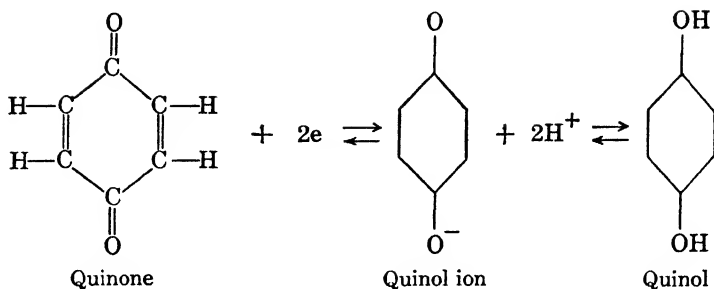
The **monooxime of quinone** is the same substance as is formed by treatment of phenol with nitrous acid (*p*-nitroso-phenol (p. 483)). As both forms probably occur in appreciable quantities in the equilibrium mixture the substance is known by both names.

Quinhydrone. Quinone has the ability to form addition compounds with a number of substances, and the resulting compounds cannot be represented by ordinary formulas. When quinol is oxidized with ferric chloride a greenish black precipitate results which is an addition compound of quinol with quinone, $C_6H_4O_2C_6H_4(OH)_2$, called *quinhydrone*. The manner in which the two molecules are bound together is unknown. It is commonly spoken of as a "molecular compound" of which other examples have been cited (p. 482).

Quinone can be reduced with sulfur dioxide in water solution to quinol, which is, therefore, frequently called *hydroquinone*.

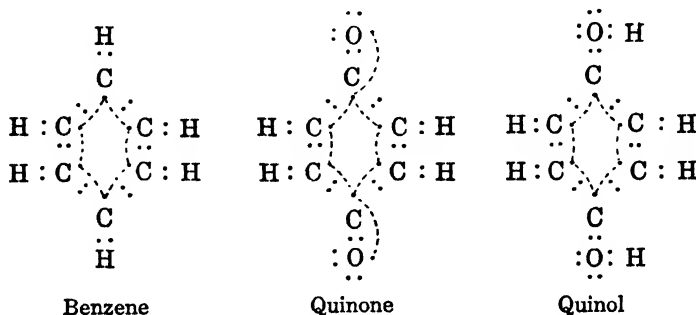
Use in Determining Hydrogen Ion Concentration. Quinhydrone has in recent years been employed extensively in determination of hydrogen ion concentration. It is not very soluble in water, and the solution to be tested is first saturated with it.

In such a solution an equilibrium exists which may be represented thus:



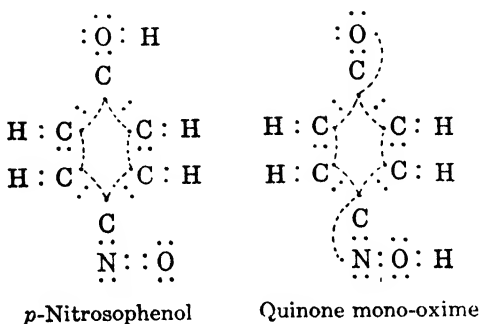
The quinol ion is extremely easily oxidized (de-electronized) to quinone and in a solution containing quinol ions there is a measurable tendency for electrons to plate out on an inactive electrode (gold or platinum) leaving the solution positively charged. Such tendency depends only on the concentration of the quinol ion. In a saturated solution containing quinhydrone the quinone and quinol concentrations remain the same and practically constant. Therefore the only variable which influences the quinol ion concentration is the hydrogen ion concentration which is to be measured. When the hydrogen ion concentration is high there are few quinol ions and hence very low difference of potential between the inert electrode and the solution. Lowering the hydrogen ion concentration increases this difference of potential. The practical use and limitations of the quinhydrone method are not appropriately discussed here. Its use has now largely been abandoned in favor of the "glass electrode" method.

The relationship between quinol and quinone is made clearer by considering the probable electronic arrangements, though adequate formulas representing these arrangements are difficult to draw. If we use the partial valence formulas for benzene, quinone and quinol pictured in electronic terms we obtain the following:

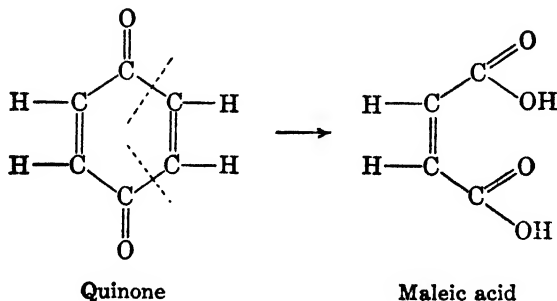


In the quinone formula there are two electrons (at bottom and top of inner hexagon) each of which may pair off in three ways. The electrons

which are represented as being unpaired on the oxygen atoms are each able to pair with one of these electrons. As soon as another electron is furnished (as in quinol) to pair with the lone oxygen electron this pairing with electrons in the ring ceases and the quinone nucleus becomes the typical benzene nucleus. This interpretation makes reasonable the fact which is observed repeatedly, that reduction of quinone derivatives yields benzene derivatives and conversely oxidation of benzene derivatives yields quinone derivatives. The fact that compounds not infrequently exist in tautomeric forms, one of which is quinoid and the other benzenoid, can also be explained on the same basis. The formulas for the tautomeric forms, *p*-nitrosophenol and quinone mono-oxime based on this interpretation are given below:

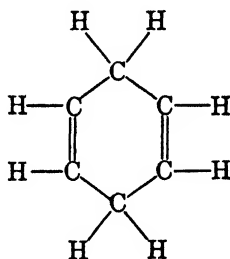


The oxidation of quinone proceeds in accordance with the general behavior of ketones (p. 116). The oxidation begins on the carbon atom which holds the oxygen, and this means that a carbon-carbon linkage must break. This happens in the following way, and with the proper oxidizing agent and conditions, maleic acid is formed, along with other products which have not been recognized.



The catalytic vapor phase oxidation of benzene yields maleic acid (p. 286) and quinone is probably an intermediate product.

Quinone Not a Typical Aromatic Compound. It will be clear from our previous discussion that quinone is not a substitution product of benzene, and does not have the stable nucleus which is characteristic of benzene and its substitution products. This does not mean that the quinone nucleus is very unstable for this is not so, as rather strong oxidation is necessary to break the ring. Quinone, though it does possess a characteristic conjugated unsaturation of its own, is not what is regarded as a typical aromatic compound. The reactions which are peculiar to those substances which have a stable nucleus, such as the direct formation of nitro compounds, sulfonic acids, etc., do not take place with quinone. Quinone may be regarded as a derivative of the dihydrobenzene which has the following formula:



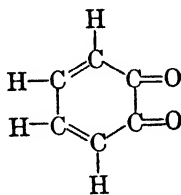
Dihydrobenzene

There is, however, a closer relationship between the quinone nucleus and the benzene nucleus than appears from this relationship.

In the oxidation of quinol to quinone there is a change from the benzene ring structure to the quinone ring structure, and in the reduction of quinone the reverse change takes place. There are numerous cases in which the transition from the "quinoid" structure to the "benzenoid" structure, and vice versa, takes place readily by oxidation or reduction. In some cases substances have tautomeric forms one of which has a quinone structure and the other a typical benzene structure. This is illustrated by the tautomeric forms, *p*-nitrosophenol and quinone monooxime. The fact that quinone derivatives are colored

and many benzene derivatives are colorless makes this change from one form to the other important.

The particular quinone which has engaged our attention is the simplest member of a class, and is called simply "quinone" and sometimes benzoquinone to show that it is related to benzene. More definitely it may be designated as *p*-benzoquinone, for *o*-benzoquinone is also known. The latter is prepared by oxidation of catechol, and is assigned the following formula.



o-Benzoquinone

It may be reduced to catechol and in other ways shows properties somewhat similar to the commoner *p*-quinones. Quinones which are related to more complex hydrocarbons than benzene will be encountered later.

PROBLEMS

1. Write the formula for the nitrogen compound corresponding to ordinary quinone.

2. Attempt to picture the structure of a *meta* quinone. Such compounds are not known.

3. The 1, 4-di-ketone derivative of cyclohexane is known, and forms an addition product with hydrocyanic acid. Why does it behave differently from quinone?

4. Color is often associated with lone or loosely paired electrons. How is the color of quinone and the lack of color of quinol explained on this basis?

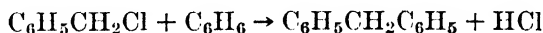
5. Is there anything about the ordinary quinone formula unlike the structure of ordinary ketones, which would preclude the possibility of its forming addition products such as, for example, with hydrocyanic acid? Does the idea of partial valence help explain why this addition does not take place?

CHAPTER XXXII

HYDROCARBONS CONTAINING MORE THAN ONE PHENYL GROUP

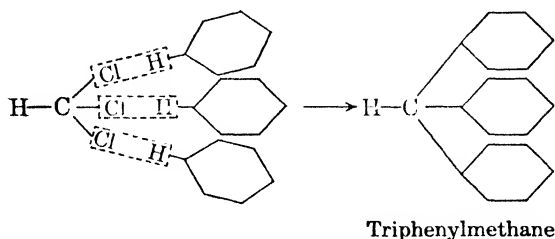
Toluene may be looked upon as methane in which one hydrogen atom is replaced by the phenyl group. This suggests the possibility of other hydrocarbons in which more than one hydrogen atom of methane is replaced by the phenyl group, and such hydrocarbons exist. It also suggests the possibility of hydrocarbons in which more than one hydrogen atom of ethane or propane, etc., is replaced by phenyl groups, and these hydrocarbons also exist. In the ethylene and acetylene series also, more than one atom may be replaced by phenyl groups. It is obvious that the number of hydrocarbons which might be derived after this fashion is very large, and since they should all yield numerous derivatives, the number of theoretically possible related compounds is even much greater. A large number of these hydrocarbons and their derivatives have actually been prepared, but we shall have to limit our discussion to those that are of technical or theoretical importance.

Diphenylmethane can be prepared by the reaction of benzyl chloride on benzene in the presence of anhydrous aluminum chloride (Friedel-Crafts' reaction).



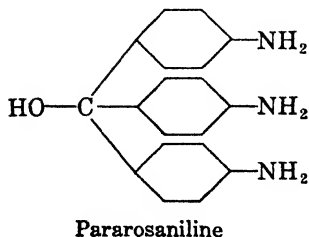
Its melting or freezing point is 26° and it boils at 263° . It has a distinct pleasant odor. When oxidized the two benzene nuclei are unaffected but the two hydrogen atoms attached to the methane carbon atom are replaced by oxygen forming benzo-phenone. As is characteristic of toluene and the other homologs of benzene, the carbon atom attached to the nucleus is not broken off during oxidation unless the conditions are extreme. Diphenylmethane forms many derivatives but they are not of particular importance.

Triphenylmethane, $(C_6H_5)_3CH$, is a colorless crystalline substance which melts at 92° and boils at 385° . It is soluble in other hydrocarbons like benzene and also in ether but is only slightly soluble in cold alcohol. It can be made by Friedel-Crafts' synthesis, using benzal chloride, $(C_6H_5CHCl)_2$, and benzene, or using chloroform and benzene. The latter reaction is preferable because of the relative cheapness of chloroform.

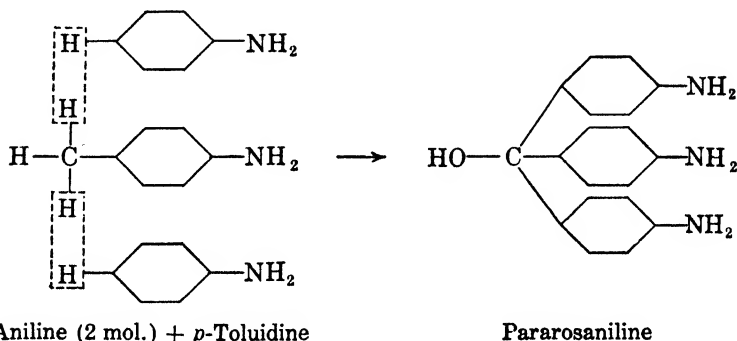


There are many derivatives of triphenylmethane which are of importance. They are not made from triphenylmethane itself as a rule, but are made by indirect methods. Phenolphthalein and fluoran which have already been mentioned (p. 518) are triphenylmethane derivatives though their manner of preparation does not suggest it.

On oxidation of triphenylmethane the one hydrogen attached to the methane carbon atom is replaced by hydroxyl. On nitration with cold fuming nitric acid a nitro group replaces each of the hydrogen atoms *para* to the methane carbon atom, and these nitro groups can be reduced to amino groups. The resulting amino compound like triphenylmethane itself can be oxidized to an alcohol which has the following structure.



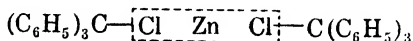
It is called **pararosaniline** and will be mentioned later in the discussion of dyes. It may be prepared by a method which is somewhat typical and at the same time involves a reaction which would not be expected from a study of simpler compounds. On mild oxidation of a mixture of *p*-toluidine and aniline (in the ratio of one molecule of the first to two of the latter), pararosaniline results. This is an example of a *para* substitution in an aniline, which we have found takes place with great ease, but is different from any that we have so far considered as it takes place simultaneously with oxidation.



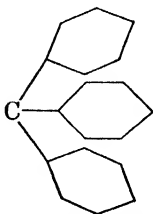
Hexaphenylethane-Triphenylmethyl. Certain derivatives of triphenylmethane are of very great theoretical interest, as they exhibit valence phenomena which are entirely unlike anything which we have so far studied. Triphenylmethyl chloride, $(\text{C}_6\text{H}_5)_3\text{CCl}$, which can be made by Friedel-Crafts' synthesis from carbon tetrachloride and benzene, is unusual in that it appears to undergo dissociation into ions to a limited extent. The corresponding bromide shows a higher ionization, as would be expected from the higher reactivity of alkyl or aryl bromides as compared with chlorides. The chloride and bromide are not isolated examples, however, as the corresponding alcohol, triphenylcarbinol, unlike alcohols generally, shows the properties of a weak base, as it gives rise to hydroxyl ions.

The triphenylmethyl group is in general unable to hold other atoms or groups (with the exception of hydrogen) in stable combination. If triphenylmethyl chloride is treated with zinc, which

might be expected to bring about a condensation to form hexaphenylethane after the manner indicated,



a remarkable hydrocarbon is formed which is thought to exist partly in the form of free *triphenylmethyl*,¹



Triphenylmethyl

in which carbon has an active valence of three. This hydrocarbon is colored and is able to conduct electricity when dissolved in certain solvents, hence is in the form of both positive and negative triphenylmethyl ions. This is an extremely unexpected behavior since atoms very seldom break off as ions from carbon atoms, and such a separation of carbon from carbon would be least expected.

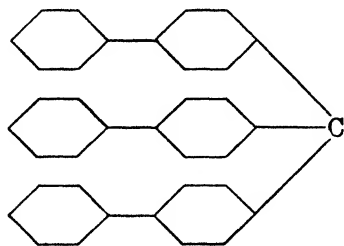
One explanation for the behavior of this hydrocarbon and its derivatives employs to some extent the idea of partial valence, as well as the valence conceptions of Werner.² According to Werner the valence of the carbon atom may be pictured as being exerted on the surface of a sphere surrounding the atom. In the case of methane the four hydrogen atoms are symmetrically arranged on the surface of the sphere, in such a way that there is no more room for other atoms to attach directly,

¹ This compound was discovered in 1900 by Moses Gomberg (1866-1947) of the University of Michigan, while attempting to prepare hexaphenylethane. From the standpoint of theory this discovery is one of the most important made since organic chemistry became a systematized science.

² Alfred Werner (1866-1920), late Professor of Chemistry in the University of Zurich in Switzerland.

though there may be some unused space which may be effective in attracting and holding other molecules in loose combination (residual valence). We have already noted that the atoms attached to the phenyl group are tightly held as are atoms held by doubly bonded carbon atoms (p. 430). In the case of triphenylmethyl the connecting carbon atoms of the phenyl groups, on account of their unsatisfied or unsaturated condition, may be pictured as "greedy" and thus each takes up more than one fourth of the surface of the sphere of the methane carbon atom. When three such groups are attached, each covering, as it were, more than a fourth of a sphere, there is not enough valency left to hold another atom or group in stable combination. Dissociation takes place in two ways forming both positive and negative ions on the one hand and two electrically neutral radicals on the other. It is to be noted, however, that triphenylmethane, $(C_6H_5)_3CH$, is stable and shows no remarkable properties in this respect; it thus appears that a hydrogen atom can be held by the triphenylmethyl group. Tetraphenylmethane, in which a fourth phenyl group is attached, is also known but is *very* difficult to prepare. The behavior of these compounds has been interpreted with some success in terms of resonance.

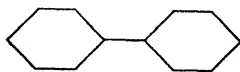
Much study has been devoted to triphenylmethyl and similar compounds, so that triphenylmethyl does not stand by itself as an isolated case, as many similar compounds have been made.³ The compound with the structure given below is more completely in the trivalent form represented than is triphenylmethyl.



Tribiphenylmethyl

³ See Chapter 6 (Bachmann) in Gilman Organic Chemistry (Second Edition), 2 vols. J. Wiley & Sons.

Biphenyl. Besides the hydrocarbons which may be regarded as derivatives of the aliphatic hydrocarbons by substitution of the phenyl group for hydrogen, there are hydrocarbons which are derived from benzene by substitution of the phenyl group for hydrogen on the nucleus. The simplest of these is *biphenyl*.

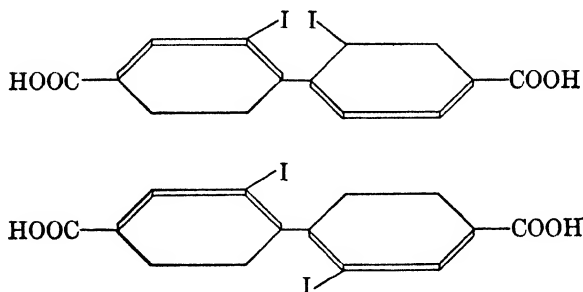


Biphenyl

An important derivative of biphenyl, known as *benzidine*, has already been mentioned (p. 473). Benzidine and its homologs, though derivatives of biphenyl, are not made from biphenyl but are made by rearrangement, from hydrazobenzenes. Biphenyl itself can be made by Fittig synthesis from phenyl bromide and sodium, and also by passing benzene vapor through a red hot tube. It is very stable toward oxidation but produces benzoic acid on extreme treatment with strong oxidizing agents.

Asymmetry Due to Restricted Rotation. A very interesting type of optical isomerism involving biphenyl and related derivatives has been investigated fully within recent years particularly by Roger Adams and his associates in this country. Perhaps the simplest compound of this type to be capable of resolution into optically active forms is represented by the models pictured below. As pictured, one structure is the mirror image of the other, and one structure cannot be superimposed one upon the other. However, if as is usually the case, there was freedom of rotation around the axis of the single bond between the phenyl radicals, the two structures would be identical. It has been amply demonstrated that groups in the *ortho* position collide in such a way as to prevent such free rotation, and that the restriction of the rotation is more or less complete depending particularly upon the size and number of groups *ortho* to the linkage between the rings. In case a number of large groups are present the restriction is complete at any ordinary temperature, and the *d* and *l* forms when separated cannot racemize. On the other hand when the groups are small the *d* and *l* forms cannot be separated at all. Intermediate between these two extremes are a number of cases in which separation can be made, but each form changes

rather readily into the other (racemizes) showing that rotation is not entirely prevented but is only hindered. This is true in the case pictured.



Asymmetric Optical Antipodes

Ordinarily two *ortho* groups are not sufficient to restrict rotation. That the compound pictured is capable of resolution shows that not only the large iodine atoms but also the *ortho hydrogen* atoms interfere with rotation. If the hydrogen atoms did not interfere, while *complete* rotation might be prevented, one ring could not be held at approximately right angles to the other, and two separable forms could not exist.

Studies of this kind, of which many have been made, throw much light on the structure, size, and shape of molecules and their constituent groups.

A large number of complex hydrocarbons such as diphenylbenzene, triphenylbenzene, and even tetraphenylbenzene, are known, as well as their derivatives, but they are not of special importance. Hydrocarbons in which there is a chain of benzene nuclei such as in dibiphenyl are also known.



Dibiphenyl

PROBLEMS

1. How many di-substituted phenyl derivatives of vinyl chloride should be possible, taking into consideration *cis-trans* isomerism?
2. Trinitrotriphenylmethane seems to show weak acid properties. How is this related to the behavior of triphenylmethyl?

3. Outline a second Friedel-Crafts' reaction that can be used to prepare diphenylmethane.

4. How many diphenyl benzenes should be possible?

5. Count up the number of valence electrons in neutral triphenylmethyl. How is this number unusual?

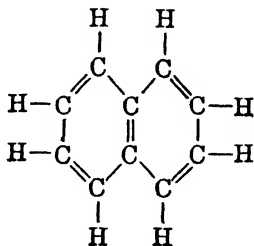
6. Benzophenone (in solution) reacts with metallic sodium to yield a colored compound and no by-products. Picture the product electronically. It is very reactive. Such a compound is known as a *ketyl*.

CHAPTER XXXIII

NAPHTHALENE AND ITS DERIVATIVES

The hydrocarbon which is the most abundant in coal tar and technically next to benzene in importance is *naphthalene*, $C_{10}H_8$. Its production in America, to a large extent for use as a source of phthalic acid and in dye manufacture, is in the neighborhood of 200,000 tons yearly. It constitutes about 6 per cent or more of coal tar, from which it is obtained as a crystalline substance melting at 80° and boiling at 218° . It has a distinctive odor which is familiar, since it is commonly sold in the form of "moth balls" as a moth repellent and insecticide. Its use for these purposes has fallen off, however, with the introduction of newer agents such as *p*-dichlorobenzene.

Structure. Phthalic acid (p. 516) is produced technically by the oxidation of naphthalene. In naphthalene, therefore, there must be two "side chains" attached to a benzene nucleus in the *ortho* position. The only way in which a reasonable structure could be pictured, fulfilling this condition, with a molecular formula $C_{10}H_8$, is by a double ring structure similar to that given below.



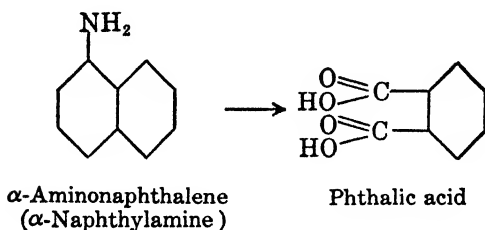
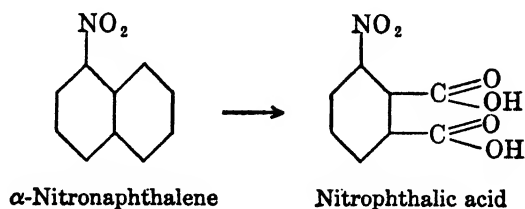
Naphthalene (Erlenmeyer¹)

Evidence that a second ring is actually present which is at

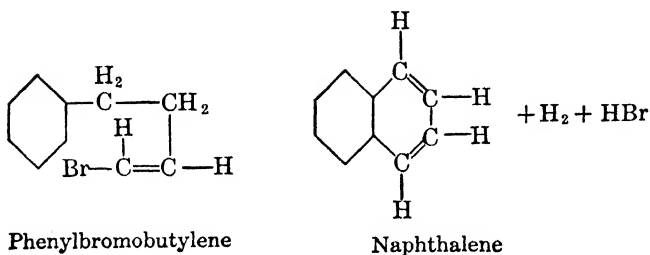
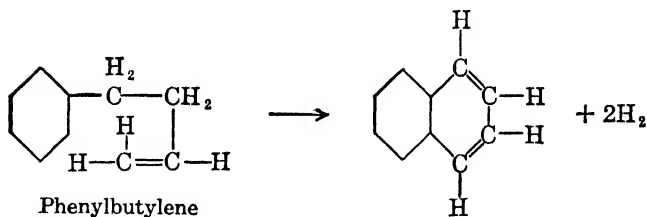
¹ Emil Erlenmeyer (1825-1909) was Professor of Chemistry in the Technical Hochschule in Munich. He designed the very useful Erlenmeyer flask.

least easily convertible into a benzene ring, is based on experiments such as the following. Naphthalene when treated with nitric and sulfuric acids forms a nitro compound analogous to nitrobenzene. If this nitronaphthalene is oxidized, a nitro substituted phthalic acid is produced, so it is obvious that the nitro group was substituted on a benzene ring. If on the other hand the nitronaphthalene is reduced to aminonaphthalene, and then oxidized, phthalic acid itself is produced. This shows that there is another ring which did not hold the nitro or amino group, which constitutes the benzene ring in the phthalic acid produced.

Using the double ring structure, these results are pictured below. The presence of the nitro group on one of the rings stabilizes it toward oxidation so that oxidation takes place on the ring not holding the nitro group. The presence of the amino group, on the other hand, makes the ring on which it is substituted more easily oxidized and therefore oxidation breaks the ring to which the amino group is attached. This is in accord with the fact that aniline is much more easily oxidized than either benzene or nitrobenzene.



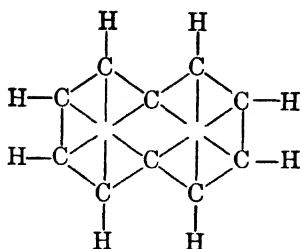
The synthesis of naphthalene from phenylbutylene or phenylbutylene bromide, indicated below, also confirms its double ring structure.



Either of the above reactions can be made to take place by passing the material over red hot lime. There are other methods of synthesis which also point to the same structure.

The structure of naphthalene is based upon that of benzene, and the exact structure of naphthalene hinges somewhat on the exact structure of benzene. All of the discussions regarding the structure of benzene including the deductions from quantum mechanics are germane here. However, the situation is somewhat different, since in a *symmetrical* naphthalene formula the double bonds cannot shift constantly in position. Whether the structure is symmetrical (both rings alike) or unsymmetrical (rings different) there is no ring that exactly duplicates the benzene nucleus with its shifting bonds. We might expect naphthalene therefore to have properties somewhat different from a compound possessing two *benzene* rings. It is, as a matter of fact, more easily reduced than benzene; it takes up four atoms of hydrogen quite readily and one of the rings becomes saturated. The product is known as *tetralin* and is produced technically for use as a solvent.

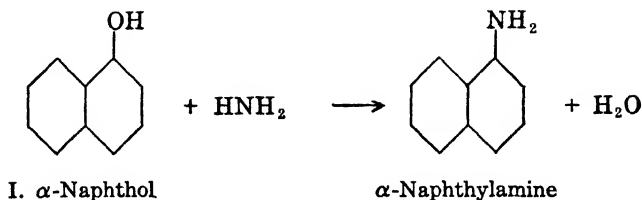
If a centric structure analogous to the one suggested for benzene is applied to naphthalene, the following formula, results.

Naphthalene (Bamberger²)

This represents naphthalene as a substance with ten carbon atoms in a ring but with two centers toward which the fourth valences of the carbon atoms are directed.

In this formula the structure is *not* equivalent to two benzene nuclei with two carbon atoms in common, since there is really no six-membered ring. It is only by the destruction or reduction of one of the rings that the other ring can become identical with a benzene nucleus. The following cases will show that the properties of the substance are in accord with these formulas in this respect.

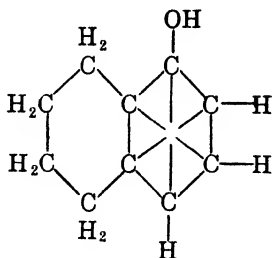
The hydroxyl derivatives of naphthalene are called *naphthols* and in many respects are similar to the phenols. In some respects they are, however, different as the hydroxyl group is not so tightly held and can be replaced by the amino group by heating with ammonia in the presence of catalysts such as zinc chloride.

I. α -Naphthol α -Naphthylamine

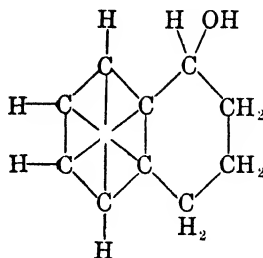
However, the compound with the formula II (below) in which the unsubstituted ring is reduced, very greatly resembles the phenols in chemical properties, in that the hydroxyl group is

² Eugene Bamberger was Professor in a Polytechnic Institute in Zurich, Switzerland.

tightly held and does not enter into such reactions as the one with ammonia.



II. *ar.* Tetrahydronaphthol



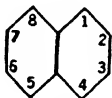
III. *ac.* Tetrahydronaphthol

The compound with the formula III, on the other hand, very greatly resembles the typical aromatic alcohols such as benzyl alcohol and does not resemble the phenols. The latter two substances are called respectively *aromatic tetrahydronaphthol*, and *alicyclic tetrahydronaphthol*, to indicate that in the first the hydroxyl group is attached to a typical aromatic ring and in the second the hydroxyl group is attached to an alicyclic (aliphatic cyclic) ring. The amino compound formed from the naphthol with formula I resembles aniline in most respects; it can be diazotized, etc. The group is not so tightly held as in aniline, however, and the substance can undergo hydrolysis. The amino compound with the formula analogous to that of II, *ar. tetrahydronaphthylamine*, resembles aniline more closely in chemical properties. The amino compound analogous to the hydroxyl compound with formula III, *ac. tetrahydronaphthylamine*, is unlike the aromatic amines but more like the aliphatic amines since it does not undergo diazotization. Naphthalene substitution products then are not exactly analogous to the benzene substitution products, though they resemble them in many respects. If one of the rings is broken or reduced, the other ring becomes a typical benzene ring.

The reason for the emphasis on this peculiarity of the naphthalene structure is to guard the student against thinking that one can, simply by drawing hexagons indiscriminantly, produce

intelligible formulas for organic compounds. Such formulas must be subjected to scrutiny.

Naming Isomeric Derivatives. As in the case of benzene a simplified formula may be used successfully for the formulation of isomeric derivatives, etc. In this case a double hexagon without any representation of the disposition of the fourth valences of the carbon atoms is satisfactory as long as the substitution products alone are dealt with. It is customary to number the carbon atoms which are able to hold substituents in a clockwise fashion as indicated³ and the naming of derivatives is simple and definite.



If a single substituent is in positions 1, 4, 5 or 8, it has the same relation to the rest of the molecule and hence represents a single substance which is commonly designated as the α substitution product. If a substituent in a monosubstitution product is in the position represented by 2, 3, 6 or 7, it is designated as the β substitution product. There are, then, according to fact as well as theory, two naphthalene monosubstitution products for each group which acts as a substituent. According to theory ten different disubstitution products are possible in case the two substituents are the same. The ten possibilities may be listed as follows: 1-2, 1-3, 1-4, 1-5, 1-6, 1-7, 1-8, 2-3, 2-6, 2-7. When the two substituents are different there are fourteen possibilities. In several cases all of the possible disubstitution derivatives have been prepared, so that the formula commonly used serves satisfactorily.

Addition Reactions, Oxidation. Naphthalene, as has already been noted, is chemically similar to benzene. However, it is more easily reduced than benzene (until one of the rings is saturated), it forms halogen addition products more readily than benzene up to the point where four atoms of the halogen are

³ The conventional methods of numbering all types of ring systems are given in the opening pages of Richter, "Lexikon der Kohlenstoff Verbindungen" and also in Patterson and Capell's "The Ring Index."

taken up and one of the rings is saturated, and it is more easily oxidized than benzene. The oxidation (mild) proceeds readily only to the point where one of the rings is broken and the carboxyl groups remain in its stead. The naphthalene structure is symmetrical as both rings are alike, and either may be reacted on. As soon as reduction, addition of a halogen, or oxidation takes place the ring which is unattacked takes on definitely the more stable benzene structure.

Position Taken by Substituents. The nitration of naphthalene produces α -nitronaphthalene. If naphthalene is chlorinated, the chlorine goes to the same position, but when naphthalene is treated with sulfuric acid, a mixture of α - and β -sulfonic acids are formed. At lower temperature the α -compound predominates and at high temperature the β -compound is formed almost exclusively. There are no simple rules of substitution by which one can predict the position that a second entering group will take. Each case must be worked out almost independently. The position taken by a second substituent depends somewhat upon the position and the character of the group already present, but in the *majority of cases*, especially if the first substitution is in the 1 position, the second substituent takes one of the similar positions, 4, 5 or 8. An outstanding exception to this statement is the case of the hydroxyl group, which in position 1 generally directs the next substituent to position 2, though in some cases the entering group goes to position 4.

The **homologs** of naphthalene, though they can be made by Fittig's or Friedel-Crafts' synthesis, are generally not technically or otherwise important.

The **halogen substitution products** with the exception of *α -chloronaphthalene* are relatively unimportant. α -Chloronaphthalene is made by direct chlorination in the presence of iron as a catalyst and is used in the manufacture of dyes. If no catalyst is present, the addition products are formed in which two or four atoms of chlorine add on. β -Chloronaphthalene is made by indirect methods. It is notable that the chlorine substituted naphthalenes as well as other substitution products of naphthalene are

more reactive than the corresponding benzene derivatives. Groups or atoms attached to the naphthalene nucleus are not so firmly held. All of the ten possible dichloronaphthalenes are known.

α -Nitronaphthalene is formed by direct nitration of naphthalene and is important because by reduction it is converted into **α -naphthylamine** which is a highly important compound in dye manufacture. The latter compound resembles aniline except in a few ways already noted, and undergoes the reactions common to this substance. Of special importance is its diazotization and coupling with phenols and anilines, by which valuable dyes are produced.

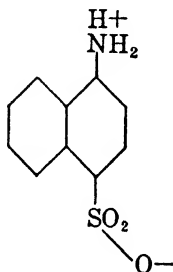
β -Naphthylamine may be made from the corresponding hydroxy compound by reaction with ammonia, which is carried out commercially by heating **β -naphthol** under pressure with a solution of ammonia and ammonium sulfite. A similar reaction may be used to obtain **α -naphthylamine** from **α -naphthol**. These reactions illustrate the fact that naphthalene substitution products are more reactive than the corresponding benzene derivatives. These reactions are reversible, so that the naphthylamines, when heated with water in the presence of an acid, undergo hydrolysis.

By the hydrolysis of **α -naphthylamine** (obtained from **α -nitronaphthalene** by reduction) **α -naphthol** is produced. This substance is also made by fusion of the corresponding sulfonic acid, which is analogous to a method for preparing phenol. As already stated the naphthols are similar to the phenols in many respects, but the hydroxyl group is more easily replaced. They are easily converted into their ethers merely by boiling with the alcohol in the presence of an acid.

β -Naphthol is more important technically than the **α** compound, and is used for dye manufacture in very large amounts. It is made from naphthalene- **β** -sulfonic acid by fusion with sodium hydroxide. It is easily converted into its methyl ether which has the odor of orange blossoms and is used under the name of *nerolin* in perfumery.

The two **naphthalene sulfonic acids** are made by sulfonating naphthalene. The α acid is formed principally at lower temperature, while the β acid is obtained by sulfonation at high temperature. These compounds are important principally because they are convertible into the naphthols which in turn can, if desired, be converted into naphthylamines.

There are a few derivatives of naphthalene in addition to the simpler ones already mentioned which are especially important in the manufacture of dyes. **Naphthionic acid** is analogous to sulfanilic acid and has the following structure.



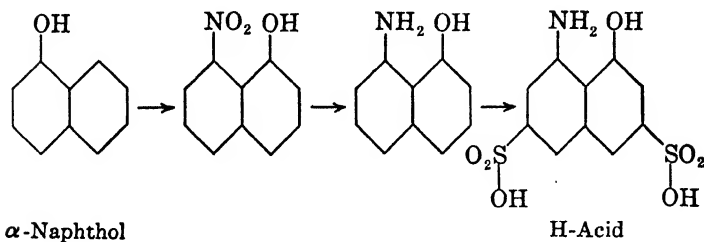
Naphthionic acid

It is made by the sulfonation of naphthylamine, in the same manner as sulfanilic acid is made from aniline. It can be diazotized like sulfanilic acid and the diazo compound coupled with phenols, naphthols, and aromatic amines to form azo compounds. In each case the azo compound formed is a dye, and in some cases the dyes produced are important ones.

R-Acid, 2-naphthol-3,6-disulfonic acid and **G-Acid**, 2-naphthol-6,8-disulfonic acid are produced together by the sulfonation of β -naphthol. R-acid gets its name from the fact that when coupled with diazo compounds red dyes are produced. (Ger. *rot* red.) G-acid also gives red dyes but with a more yellow tinge. (Ger. *gelb*, yellow.)

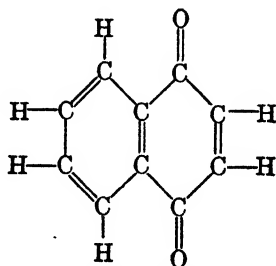
H-Acid is more important than either of the two preceding from the standpoint of the amount produced in this country. It is 1-amino-8-naphthol-3,6-disulfonic acid. It is produced by

the nitration of α -naphthol followed by reduction to the amine and the introduction of two sulfonic groups.



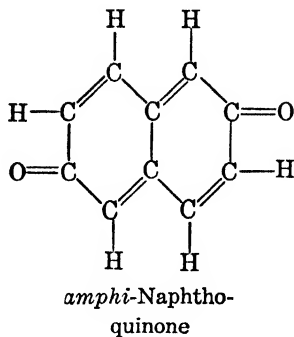
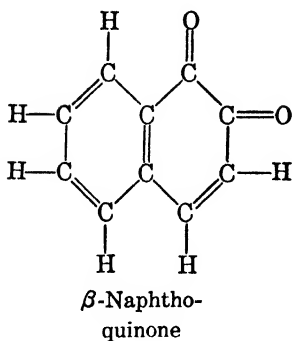
It can be diazotized and coupled with phenols or coupled directly with diazo compounds, etc. It is particularly important in the manufacture of black dyes, though many different shades are made from it.

Of some theoretical interest are the quinones related to naphthalene. α -Naphthoquinone, as it is called, is made by the direct oxidation of naphthalene, α -naphthylamine, and several disubstitution products of naphthalene in which the two substituents are in the 1, 4 position.



α -Naphthoquinone

Walnut hulls contain *juglon* (α -hydroxynaphthoquinone) which has the properties of a dye. A derivative of naphthoquinone with hydroxyl groups in the 5 and 6 position, is easily converted into a dye of some importance known as *alizarin black*. "Vitamin K" (p. 600) is a derivative of naphthoquinone. Other quinones with the formulas given below are also known.



PROBLEMS

1. Which would have the stronger acid properties, *ac.* tetrahydronaphthol or *ar.* tetrahydronaphthol?

2. If the two rings in naphthalene were unlike, what effect would it have on the number of possible monosubstitution products?

3. How many homologs of naphthalene with the formula $C_{12}H_{12}$ would be possible?

4. Work out the fourteen possible structures of naphthol sulfonic acids. Ten are known.

5. Write the formulas for (1) R acid, (2) G acid, (3) 1-amino-2-naphthol-4-sulfonic acid.

6. What products would you expect to get by the strong oxidation of α methylnaphthalene.

7. Do aliphatic amines generally undergo hydrolysis under any conditions? Why is it an easier laboratory procedure to heat α -naphthylamine with water than it is to heat a simple alkyl amine with water?

8. Is there one typical benzene ring in the α -naphthoquinone structure? Could the centric type of formula be used to represent its structure?

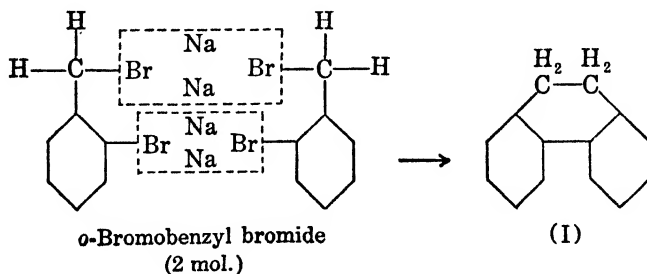
9. α -Nitroso- β -naphthol is identical with β -naphthoquinone mono- α -oxime. To what is this relationship analogous among the benzene derivatives? The compound is an acid and is used for the precipitation of cobalt in qualitative analysis.

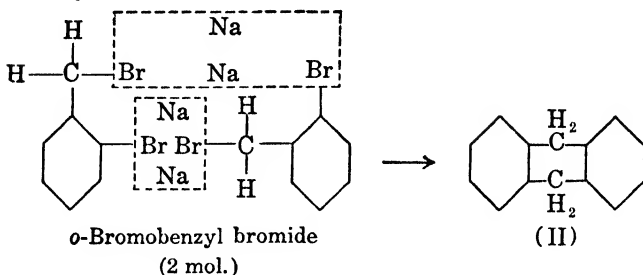
CHAPTER XXXIV

ANTHRACENE AND ITS DERIVATIVES; OTHER HYDROCARBONS

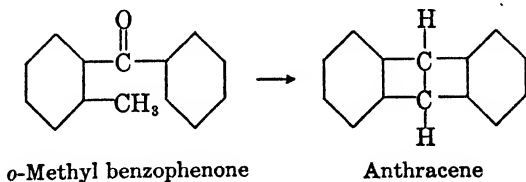
Two isomeric hydrocarbons with the formula $C_{14}H_{10}$ are found together in the high boiling fractions of coal tar. Their boiling points are too close together (340° and 351°) to make their separation by fractional distillation practicable, but they can be separated by their difference in solubility in carbon disulfide. The more important hydrocarbon, known as *anthracene*, is not very soluble while the less important *phenanthrene* is quite soluble.

Structure of Anthracene. One of the outstanding properties of anthracene is its ability to form a hydride, $C_{14}H_{12}$. The structure of anthracene is best established by the synthesis of anthracene hydride. Anthracene hydride is formed along with phenanthrene by a Fittig synthesis from *o*-bromobenzyl bromide, $C_6H_4(Br)CH_2Br$. It will be recalled that one of the advantages of the Fittig synthesis is the fact that experience has shown that migration of groups from one position to another does not take place during the course of the reaction. The Fittig synthesis in this case might take place in either of the two ways indicated.

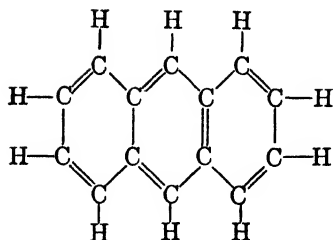




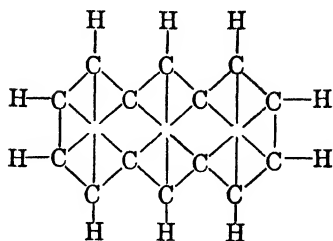
Either formula I or formula II, if no migration has taken place, represents the structure of anthracene hydride. That formula II represents anthracene hydride is indicated by the fact that the *o*-methyl benzophenone (*o*-tolylphenylketone) yields anthracene itself when heated with zinc dust. This reaction can easily be pictured as forming a compound with a structure similar to formula II but could not produce a substance with a formula similar to I.



This synthesis seems to show that there should be a "para-bond" in the central ring of anthracene, and such a formula has been proposed and used. However, the evidence for the structure of anthracene is not based on these reactions alone, as both anthracene and anthracene hydride may be produced in other ways which are in accord with the structures which are indicated by these reactions. The disposition of the fourth valences of the carbon atoms is a problem in the case of anthracene as in benzene and naphthalene. The structure of anthracene is generally represented by one of the two formulas given below.

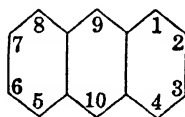


Anthracene (I)



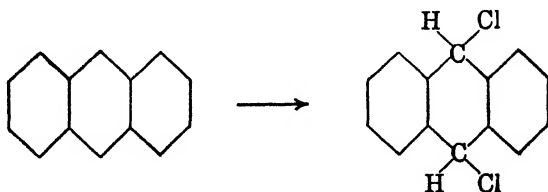
Anthracene (II)

Whenever resonance enters into play (p. 135) it is impossible to represent a compound adequately by a single formula. Anthracene doubtless represents a complex resonating system and it is even more difficult to construct a reasonably acceptable single formula for it than for benzene or naphthalene. As in the case of benzene and naphthalene, the hexagons can be used without any disposition of the fourth valences, and the formula used in this way is satisfactory for the designation of isomeric substitution products. The different positions are customarily numbered as indicated.

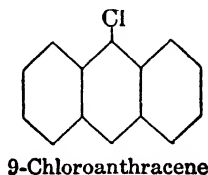


There are three monosubstitution products possible and fifteen disubstitution products if the substituents are the same.

Reaction with Chlorine. Not only does anthracene form a dihydride easily but also adds on two chlorine atoms readily.

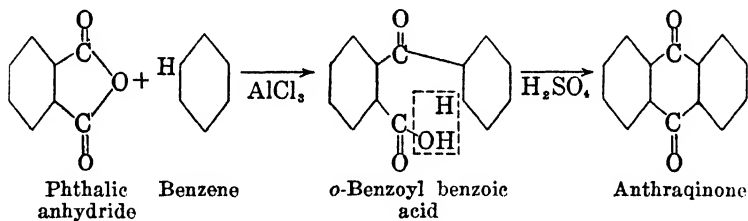


When the chlorine addition compound is treated with sodium hydroxide, hydrogen chloride is eliminated from the molecule and a monochlorine substituted anthracene is formed.



The 9-10 dichloro *substitution* product is made by the action of chlorine on anthracene at about 100°.

Anthracene is rather easily oxidized to one of its most important derivatives, **anthraquinone**, which, however, is also made for technical use by synthesis as indicated below:

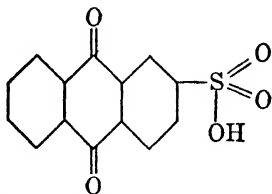


This is a stable substance and hence does not closely resemble the other quinones in chemical characteristics. Although its structure contains two benzene nuclei and appears to be that of a typical diketone, it does not ordinarily form addition compounds. This indicates that the residual valences on the carbon atoms are conjugated.

The importance of anthraquinone is based largely upon the fact that from it *alizarin* is made, although it is used to some extent for the preparation of other similar dyes.

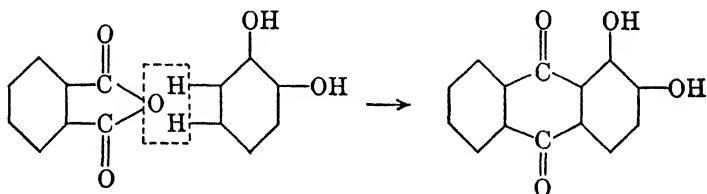
Alizarin is a red dye sometimes known as *Turkey red*, which used to be obtained from madder root and other vegetable extracts. It has been used as a dye since ancient times. With the rise of organic chemistry the structure of alizarin has been determined and it is made now from anthraquinone rather than

from plant extracts. When anthraquinone is heated with sulfuric acid it forms largely the β -(2) monosulfonic acid.



Anthraquinone- β -sulfonic acid

When this is fused with alkali and at the same time oxidized with potassium chlorate, a dihydroxy compound is formed, which is alizarin. The structure of alizarin has been determined by its synthesis from phthalic anhydride and catechol and by a study of the products produced from it by nitration. The synthesis is thought to take place in the following way which bears a slight resemblance to the formation of a phthalein (p. 518).



Phthalic anhydride + Catechol

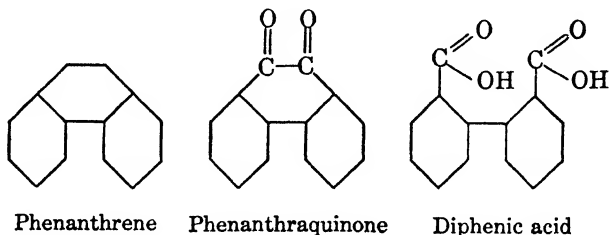
Alizarin

Other dyes closely related to alizarin are of more importance at present than alizarin itself. They are made from anthraquinone by nitration, sulfonation, etc. Natural madder extracts contain in addition to alizarin another dye, *purpurin*, which is 1,2,4-trihydroxyanthraquinone.

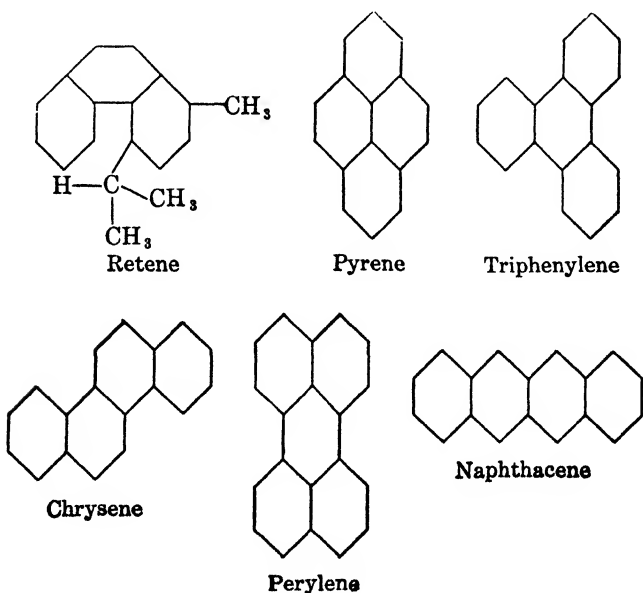
Phenanthrene, as has already been mentioned, occurs with anthracene in coal tar. It is formed along with anthracene hydride when *o*-bromobenzyl bromide is treated with metallic sodium. Probably phenanthrene hydride is first formed, and then loses hydrogen to form phenanthrene. Phenanthrene is technically unimportant, as no important uses for it have been discovered.

A number of biologically important compounds are more or less related to phenanthrene in structure. Some of these will be mentioned in Chapter XXXVIII.

On oxidation phenanthrene first yields *phenanthraquinone*, with the formula indicated. Further oxidation yields *diphenic acid*.



Retene is a homolog of phenanthrene which is found in wood tars. It is a methylisopropylphenanthrene with the structure given below. Hydrocarbons whose structures are represented in an abbreviated way below are also known.



PROBLEMS

1. According to structure I (p. 553) given for anthracene, what different kinds of rings are present? Would the formation of a hydride by the breaking of one of the rings be expected?

2. Work out from the abbreviated formulas the molecular formulas for chrysene and perylene. Are these hydrocarbons isomeric? Calculate the percentage of carbon in each.

3. Acetylene tetrabromide and benzene in the presence of anhydrous aluminum chloride produce anthracene. Picture the reaction.

4. By heating with sodium hydroxide anthraquinone yields two molecules of sodium benzoate. Picture the reaction.

CHAPTER XXXV

DYES—INDICATORS

Dyes

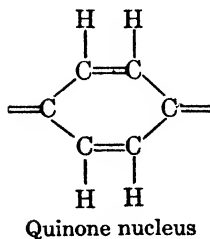
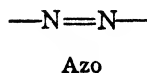
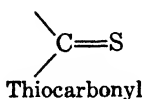
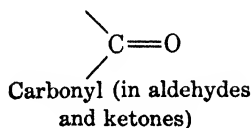
Relation Between Chemical Constitution and Color. Before we can properly discuss the color of compounds it will be desirable to refresh and clarify our ideas as to what is meant by a colored substance. Visible light is limited to vibrations of certain wave lengths which lie within rather narrow limits. We cannot see vibrations in which the wave length is longer than about 7600\AA (.00076 mm.) or shorter than about 3900\AA (.00039 mm.), but wave lengths outside these limits can be studied photographically. When the wave length is longer than visible light it is *infra red*, when shorter it is *ultra violet*. A mixture of all of the wave lengths of visible light is what we call white light. If the longer visible wave lengths (red) are absent from a light, it appears blue green, which is the complementary color of red. This blue green light when mixed with the red makes white light. If some of the shorter visible wave lengths (violet) are absent from a light, it may appear orange, which is then complementary to the missing color.

Colored substances act as screens, and take out by absorption some of the wave lengths; thus what is allowed to pass is not white light. If light which has passed through a permanganate solution is broken up into its components, dark bands or regions will show in which there has been absorption. This is called an absorption spectrum. Some substances appear perfectly colorless but absorb ultraviolet rays, and thus may be said to be colored only so far as the ultraviolet region is concerned. In the case of these substances (benzene is a good example) a modification of the molecules, such as that brought about by the formation of substitution products, may cause a shifting of these absorption bands from the ultraviolet region into the violet end of the visible spectrum. The derivative then appears yellow. Further shifting

of the absorption bands by further alteration of the molecules may cause the substances to appear orange, then red, blue, and violet.

The majority of aliphatic compounds do not absorb light either in the immediate ultraviolet region or the visible region though some substances, particularly ketones and di-ketones, show absorption bands in the invisible and sometimes in the visible spectrum. Benzene and its derivatives always show absorption either in the ultraviolet or in the visible spectrum. While the color or lack of color of compounds cannot always be predicted with accuracy, it has been found that a condition of unsaturation is an important factor in promoting color, though obviously there are other factors since simple unsaturated substances are not colored except in the extreme ultraviolet range.

The color of different organic compounds may generally be ascribed to the presence of certain groups commonly known as *chromophore* groups (from Greek, color bearer). Groups which commonly promote color are the following:



The last two are particularly important and are the most important chromophore groups appearing in the structure of dyes. There are also a number of other groups in which double bonds are present which are classed as chromophore groups. The nitro group is sometimes classed as a chromophore group, since nitrobenzene is distinctly colored. However, the nitro group itself is not wholly responsible for the color because some other nitro

compounds are colorless. The nitro group in fact only shifts the absorption bands which are present in benzene into the visible region of the spectrum. Colored substances whose structures contain chromophore groups are spoken of as *chromogens*.

Cause of Color. Just what is the cause of the production of color by these groups is not entirely clear as it is dependent on a number of factors, including the arrangement of the groups, and their unsaturation. The actual absorption of light vibrations by molecules is thought to be a phenomenon of resonance, analogous to the familiar phenomenon associated with sound. It is well known that if a certain key of a piano is struck the vibrations set up will cause the vibration of any other nearby object which has the same natural vibration rate. Thus a part of the energy of vibration is taken up by the object which is set in vibration. A sound vibration of certain wave length will be damped by any object with which it comes in contact which has the same natural vibration rate. So in the case of the light vibration; it is damped or absorbed only by objects having the same natural vibration frequency as the particular light vibration.

The absorption of light waves is thought to be due to electrons which have the same vibration frequency as the particular wave length absorbed. In the case of benzene, for example, the only electrons which have a vibration frequency capable of absorbing light are electrons with rapid vibration rates, and hence only ultraviolet light is absorbed. In nitrobenzene the natural vibration rate of some of the electrons is less rapid and they are able to absorb the shorter wave lengths of visible light and to be set in vibration. By such means light causes certain chemical reactions to take place. Only those wave lengths that are absorbed cause chemical change. The electrons which absorb the light vibrations are thought to be very limited in their vibration amplitude. Loosely bound or incompletely paired valence electrons such as are present in a double bond, may fail to reach a stable position. They are thus capable of being thrown into vibration by light, with the consequent absorption and stopping of the light of a particular wave length.

What Constitutes a Dye. The fact that a substance is colored or even intensely colored does not alone make it useful

as a dye because it is necessary that a dye adhere to the fabric and not wash out or fade. To be a useful dye the substance must be as stable as possible toward the light; that is, the vibrations set up by the absorbed light must not decompose the dye. This stability is a relative matter and it is unnecessary for the dye to last longer than the fabric on which it is to be used. The necessary property of sticking to the fabric which must be possessed by every dye is associated with the presence of acidic or base-forming groups, such as the hydroxyl (phenolic), amino, substituted amino, and sulfonic groups. These are called *auxochrome* groups (Greek, to increase color) because the introduction of these groups into a colored substance (chromogen), in addition to making it a dye, often greatly intensifies the color. The function of the auxochrome groups is illustrated by the case of azobenzene, $C_6H_5N_2C_6H_5$, which is a red substance but does not adhere to fabrics, and aminoazobenzene, $C_6H_5N_2C_6H_4NH_2$, which is a basic substance and can be used as a dye. Similarly, trinitrobenzene, $C_6H_3(NO_2)_3$, is colored, but does not dye, while picric acid, $C_6H_2OH(NO_2)_3$, dyes wool and silk directly.

In the case of wool and silk, which are protein in nature, and hence amphoteric (p. 318), it is easy to see why these acidic or basic groups might cause the dye to adhere to the fabric. It is apparent that neutralization and salt formation might result, forming in the case of an acid dye, the protein salt of the dye, and in the case of a basic dye, what might be termed a "dye protein-ate." It is thought generally that this is what really takes place when silk or wool is dyed. The correctness of this idea is borne out by the fact that, as a general rule, cotton, linen and other fibers which are not protein in nature do not dye directly like wool and silk, and may require the use of a mordant as explained later. Sometimes, however, cotton may take up a dye directly and hold it in relatively stable combination. This is commonly ascribed not to salt formation but to adsorption (p. 317) of the dye molecules on all surfaces of the fibers, in a type of combination which is on the borderland between physical adhesion and chemical combination. Though definite salt formation could hardly take place, the ability of the dye to adhere to the cellulose

fabric is conditioned by the presence of auxochrome or salt-forming groups.

A useful dye then must be an intensely colored substance, which does not fade too readily in the light, and which unless it is made within the fibers of the fabric (p. 563) has salt-forming groups and is thus able to adhere to a fabric. In addition the usefulness of a particular dye may depend on the cheapness with which it can be made and the desirability of the color produced.

Uses of Dyes. Dyes are used in largest amount for the coloring of textiles of various kinds, but this is by no means the only use to which they are put. Dyes are also used to color leather and leather substitutes, paper, cellophane, and to some extent in the manufacture of paint pigments. They are used in inks, bluing and in various kinds of shoe polishes and in the manufacture of cosmetics. In coloring foods certain non-poisonous dyes are commonly used, such as for the dyeing of margarines, butter, sausage casings, flavoring extracts, fruits, such as "maraschino" cherries, candies and other confections.

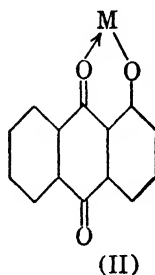
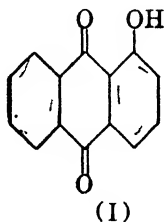
Direct Dyeing of Wool or Silk. Simple contact between wool or silk and the hot solution of a dye is sufficient to dye the cloth so that washing will not remove the color. As stated above there is good reason to think that there is salt formation between the dye, which must be either acidic or basic, and the protein material which is amphoteric. These salts, like others formed from proteins by the action of heavy acids and salts of heavy metals, are insoluble and do not wash out of the fabric. It is probable that the phenomenon of adsorption also plays a part in fixing the dye on the silk or wool fabric. Dyeing cotton directly without a mordant is applicable only in a limited number of cases.

Dyeing with a Mordant. If cotton cloth is soaked with a solution of aluminum acetate, the salt diffuses through the fibers which are permeable to such salts. If this aluminum acetate which is throughout the fibers is brought in contact with steam, it hydrolyzes and aluminum hydroxide is precipitated within the fibers, where it remains because of its insolubility. The aluminum hydroxide (or basic acetate) precipitated in this way in the fibers is called a *mordant*. It may react with acid dyes to form aluminum salts of the dyes, which are insoluble and remain in

the fabric. Hydroxides of different metals such as iron and chromium may be used in like manner. The color of the cloth after dyeing depends in many cases upon what mordant is used, as the different mordants give different shades with the same dye. When it is desired to use a basic dye on cotton the fibers may be mordanted with a heavy acid such as gallotannic acid, which forms insoluble salts with dyes.

If aluminum hydroxide is precipitated in a dye solution in the absence of any textile, the dye becomes attached to the aluminum hydroxide in the same way as in the fabric. This colored precipitate is called a "*lake*." Some paint pigments consist of finely ground colored precipitates of this type.

It is worthy of note that the "salts" which are formed by interaction of dyes and mordants, whether this takes place within a fabric or in the formation of a "*lake*," are of unusual stability toward hydrolysis. It is believed that this is due to the formation of chelate rings (p. 237). Among the most important types of dyestuffs which are used with mordants are those derived from anthraquinone and which possess the grouping I



and can form a chelate ring as pictured in II. The exact structures of the chelate compounds which are formed in the case of individual dyes and mordants are unknown but it seems very likely that "chelation" is a very important factor in most cases.

Ingrain Dyeing. In some cases dyes are actually made within the fibers which are to be dyed. This is accomplished by saturating the cloth with one of the materials necessary to make the dye, and transferring it to another solution containing the other material from which the dye is to be made, thus causing dye forma-

tion within the fibers. Similar to this procedure is that of *vat dyeing* in which case the fabric is saturated with a substance which on exposure to oxygen of the air is converted into a colored dye. In the case of either ingrain dyeing or vat dyeing the dye is formed within the fibers from which it is removed with difficulty.

Manufacture of Dyes. The manufacture of dyes is an industry of much greater dimensions than is often supposed. As has already been made clear, the products obtained from coal tar form the basis from which dyes are derived. There are, however, many steps between the "crudes" (hydrocarbons, etc.), which are obtainable from coal tar, and the final dyes. There are many substances which are prepared from these coal tar materials which in turn are used to make dyes, and these are called *dye intermediates* (German, *Zwischenproducte*). Some firms make a business of preparing certain dye intermediates, which are sold to dye manufacturers, while other firms may manufacture intermediates for their own use. There are about 500 different dye intermediates, so that it is obviously impossible to discuss here even those which may be regarded as the important ones. In the accompanying table are listed a few of the most important intermediates with their U. S. production figures given in round numbers.¹

Some of the compounds listed notably phenol, salicylic acid, diphenylguanidine, dichlorobenzene, and cresylic acid, have other important uses aside from dye manufacture. The increases in the case of phenols and phthalic acid and anhydride are attributed to their increased use in "synthetic resins."

The actual number of dyes which are in use is not known. There are thousands of names under which dyes are sold but in many cases the same dye is sold under different names, or the same dye with a different grade of purity is called by a distinctive name. There are some dyes whose method of manufacture is kept secret, others are mixtures, and the constitutions of many

¹ Most of the data on the production of dyes and intermediates was obtained from U. S. Tariff, Commission booklets, "Census of Dyes and Other Synthetic Organic Chemicals" (1928), (1938), Gvt. Printing Office, and "Chemical Facts and Figures" 2nd Edition (1946), Manufacturing Chemists' Association of the U. S., Washington, D. C.

have not been established. There are various methods of classifying dyes, based upon the method of application, or upon whether they are acid or basic, or upon their constitution. There are over twenty different classes of dyes, classed according to their constitution, and space will permit the mention of only a few of the more important types. The following are some of the most important dyes from the standpoint of production in the United States. The first three are produced in largest amounts.

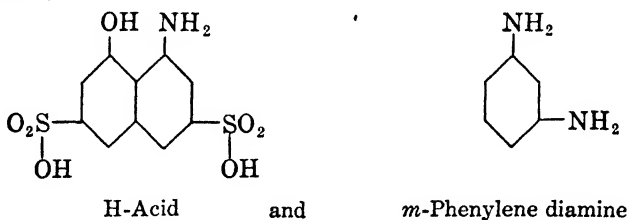
DYE INTERMEDIATES

Name	Production (lbs.)		
	1928	1938	1945
Acetanilide	1,500,000	410,000	7,000,000
1-Amino-2-naphthol-4-sulfonic acid...	967,000	351,000	1,120,000
H-Acid	3,200,000	2,516,000	3,923,000
Aniline	30,000,000	26,750,000	87,195,000
Benzidine	740,000	957,000	1,878,000
Cresylic acid	11,400,000	20,896,000
Chlorobenzene	18,000,000	237,667,000
<i>p</i> -Dichlorobenzene	4,000,000	13,000,000	26,545,000
Dichloroaniline	3,100,000	86,000	296,000
Dimethylaniline	3,700,000	2,740,000	7,041,000
Dinitrobenzene	1,700,000	1,300,000
Dinitrochlorobenzene	6,200,000	4,936,000
Dinitrotoluene	5,000,000
Diphenylguanidine	1,900,000	1,115,000	2,948,000
Dibutyl phthalate	3,130,380	4,206,000	45,915,000
<i>o</i> -Ditolylguanidine	1,300,000
Maleic acid and anhydride	1,539,000	7,700,000
Naphthalene	25,000,000	38,000,000	77,259,000
α -Naphthylamine	2,700,000	2,155,000	4,294,000
β -Naphthylamine	729,000
β -Naphthol	(1924) 3,700,000	20,983,000
Naphthionic acid	1,300,000	1,737,000
1-Naphthylamine-3,6,8-trisulfonic acid (Koch's acid)	3,600,000	3,260,000
Nitrobenzene	43,000,000	36,900,000	116,209,000
Phenol	10,200,000	44,550,000	205,112,000
Phenylglycine	4,205,000	4,412,000
Phthalic acid and anhydride	6,000,000	27,650,000	125,033,000
Salicylic acid U. S. P.	2,500,000	3,330,000	5,411,800
Sulfanilic acid	1,600,000	1,503,000	2,225,000

Sulfur black is classified as a sulfur dye, and is of unknown constitution. It is made from 2,4-dinitrophenol by fusion with sulfur or by heating with sodium polysulfide. The intermediate,

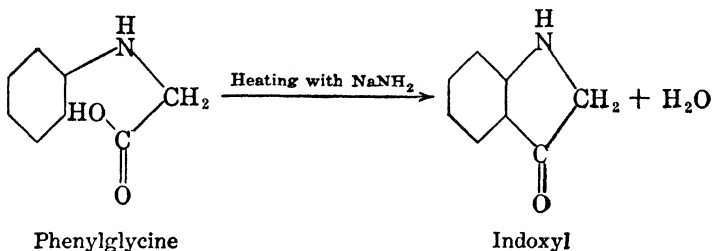
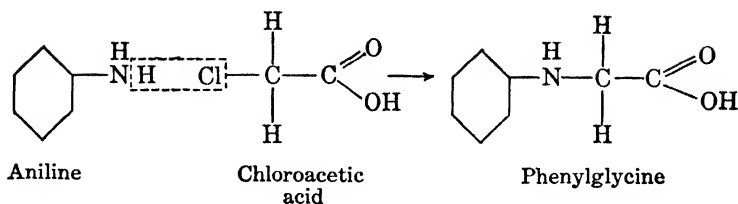
2,4-dinitrophenol, is made by heating dinitrochlorobenzene with sodium carbonate solution, which brings about hydrolysis. Frequently dyes are associated in the popular mind with bright colors but statistics show that the black dyes are the most important. A black dye is likely to be of a complex nature since it absorbs all wave lengths of light. In a complex molecule one part may absorb light in the violet end of the spectrum, another part in the red end, another part in the middle portion, in which case the resulting compound is black. About twelve million pounds of sulfur black were made in United States in 1945. It is one of the cheapest of dyes. Two less important sulfur dyes, Sulfur Blue and Sulfur Brown, are each produced in amounts totalling over a million pounds a year.

Direct Deep Black, EW, is made from benzidine, $\text{H}_2\text{NC}_6\text{H}_4\text{-C}_6\text{H}_4\text{NH}_2$,

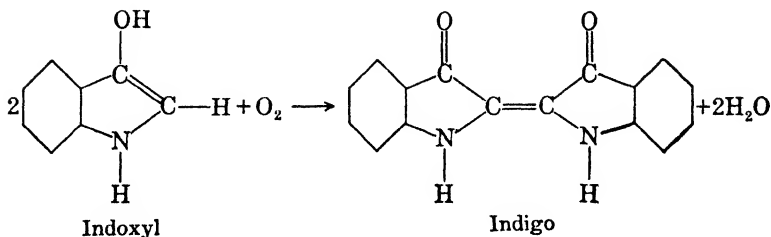


and is a complex dye. It has two azo groups in its structure and hence is classed as *bisazo dye*. About eight million pounds were produced in 1945 in United States.

Indigo has been used for thousands of years as a dye, and is still important as shown by the fact that over 13 million pounds of 20 per cent indigo paste were manufactured in this country in 1945. Part of this was converted into derivatives. Indigo was obtained by the ancients from the leaves of the indigo plant in which it occurs in the form of a glucoside *indican*. Indican undergoes hydrolysis by enzyme action and produces *indoxyl* and glucose. Indoxyl on exposure to the air oxidizes to form *indigo* or *indigo blue*. Material obtained from this natural source is not pure but contains a number of derivatives of indigo. Indigo is now made synthetically by several methods, of which the one indicated below is the most important.

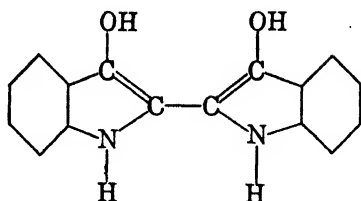


Indoxyl is readily oxidized to indigo even by atmospheric oxygen. The oxidation is accompanied by condensation.



Indigo has been synthesized in several other ways, all of which indicate that it has the structure given above. It will be noted that it is a di-ketone and has a pair of doubly bonded carbon atoms in its structure as well which gives it a structure resembling somewhat that in a quinone nucleus.

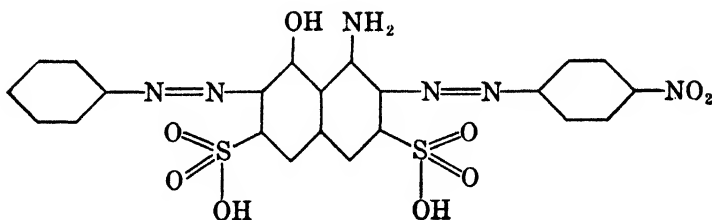
Indigo is insoluble and hence cannot be directly applied as a dye. It is converted by reduction to a colorless soluble substance known as *indigo white*, which does not possess the color bearing di-ketone structure.



Indigo white

Dyeing with indigo is accomplished by soaking the fabric in a solution of indigo white and then exposing it to the air. The indigo white is oxidized in the fabric by the air to the insoluble indigo blue which remains as a fast dye. This type of application is known as "vat dyeing" and indigo is the most important example of a vat dye.

Acid Black 10B is made from aniline, II-acid, and *p*-nitroaniline and has the structure:

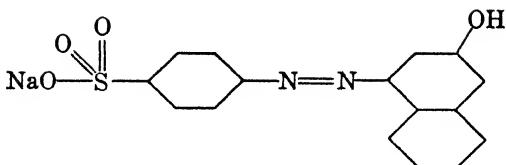


Agalma black 10B

(Production in U. S. in 1945 about 1,400,000 pounds)

Nigrosine (water soluble) is made by sulfonation of a less important dye, *spirit soluble nigrosine*, which may be made from aniline and nitrophenol. Its structure is unknown. About 1,000,000 pounds were made in America in 1945.

Orange II is made by diazotizing sulfanilic acid and coupling with β -naphthol. Its structure may be represented by the formula:

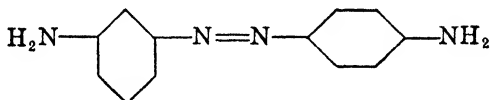


Orange II

It is a comparatively simple azo dye, and its color accordingly resembles that of the simpler colored compounds which are generally yellow. The production in United States was 1,366,000 pounds in 1945.

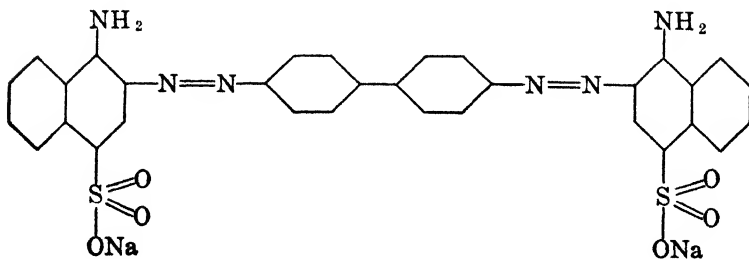
Direct blue 2B is made by diazotizing benzidine and coupling with two molecules of H-acid. The production was about 994,000 pounds in 1945.

Chrysoidine Y is a yellow dye with the structure indicated below. It is made by diazotizing *m*-phenylenediamine and coupling with aniline. The production in 1945 was about 444,000 pounds.



Chrysoidine Y

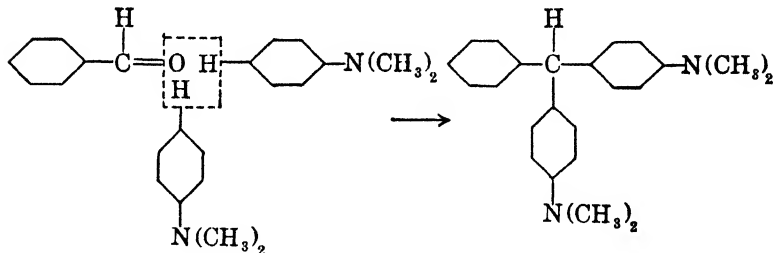
Congo red made by diazotizing benzidine and coupling with two molecules of naphthionic acid.



Congo red

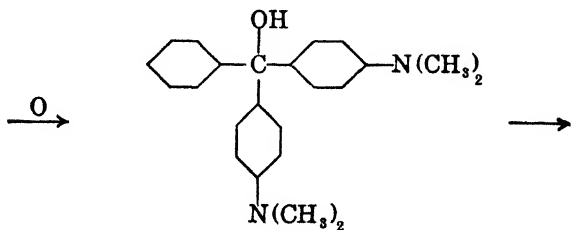
This dye is one which is especially valuable because it can be used for dyeing cotton directly without a mordant. The dye is not very stable to acids as the sulfonic acid may be freed from the salt, producing a blue color. Congo red is sometimes used as an indicator in acid-base titrations. The production of this dye was reported at 712,000 pounds in 1928. It has two azo groups (—N=N—) and is hence a diazo dye.

Malachite green is produced in less amount than any dye so far mentioned (212,000 lbs. in 1945). The reason for including it in the discussion is the fact that it is one of the simplest and at the same time one of the most important of that group known as the triphenylmethane dyes. These dyes are of theoretical as well as practical importance. Pararosaniline, already mentioned, also belongs to this class. Malachite green is made from benzaldehyde, and dimethylaniline, by the reactions which are pictured below.

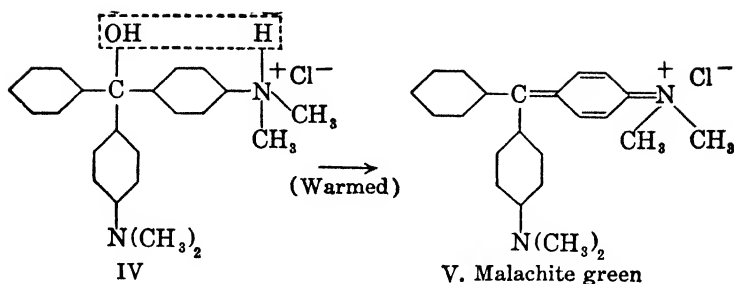


I. Benzaldehyde
Dimethylaniline (2 mol.)

II. Leuco-
malachite green



III



It will be noted that until the last reaction which is pictured takes place, there is no chromophore present in the molecule, and in fact all of the products formed up to this point are colorless. Malachite green is a basic dye and is sold in the form of its oxalate. In common with other triphenylmethane dyes it can be reduced to a colorless substance. In this case the substance formed by reduction is that pictured in formula II above. The salt of this base, after oxidation, splits off water as indicated above to form malachite green. The colorless reduction product of malachite green is called *leuco-malachite green*. (Greek, *leuco*, white.) Similar compounds related in a similar manner to other dyes are called *leuco* compounds.

Methyl violet is at present the most important triphenylmethane dye. Aside from malachite green it is the most expensive dye of those listed. About 1,003,000 pounds were produced in 1945. It is thought to be equivalent in structure to pararosaniline (p. 533) with five methyl groups substituted for the hydrogen atoms of the amino groups. The introduction of the methyl groups increases absorption in the red region of the spectrum, and thus gives the dye a violet color.

Indicators

A large number of dyes including several of those already mentioned can be used as indicators in acid-base titrations, due to the fact that they change color in passing from an alkaline to acid condition and vice versa. Inasmuch as there are a large number of such substances it will not be possible to mention or discuss more than a few.

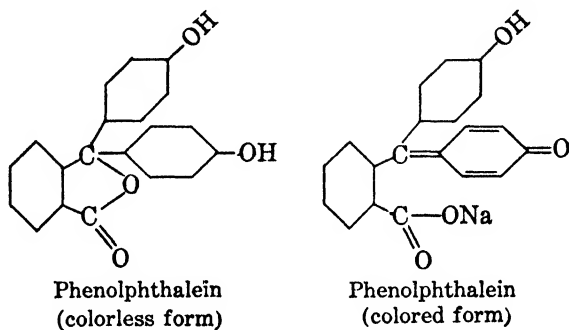
Litmus is a complex mixture which is of vegetable origin; it is obtained by extraction from certain lichens. One of the principal coloring matters present in the extract is called *azolitmin*. Litmus is a useful indicator as it changes color abruptly very close to the neutral point. When specially purified it is quite sensitive. Litmus is thought to be a mixture of acids which are themselves red, but in the form of salts are blue. The change in color from red to blue probably accompanies the change from the acid forms which are little dissociated to the salts which are highly dissociated. It may be that tautomeric changes accompany the ionization, and are responsible for the change in color.

Phenolphthalein, which has already been mentioned, is a well-known and much used indicator. Its particular advantage is the fact that it can be used in the titration of a weak acid against a strong base. In such a titration the point of absolute neutrality is not the desired endpoint. What is desired is rather the point at which there is an equivalent amount of the acid and the base, which is a slightly alkaline solution, due to the hydrolysis of the salt. The pink color of phenolphthalein does not appear until this slightly alkaline condition is reached. For this reason phenolphthalein is useful in titration of weak acids, or, in other words, is sensitive to weak acids. Acids which are extremely weak cannot be titrated by the use of phenolphthalein or any other indicator, because their salts hydrolyze so freely that the solution resulting from the presence of equivalent quantities of the very weak acid and strong base is markedly alkaline.

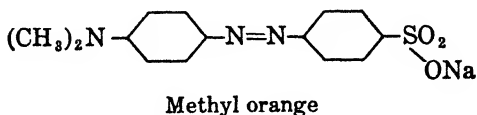
Phenolphthalein is colorless, as would be expected from the formula given previously, which contains no chromophore group. In the presence of alkali it forms a salt and at the same time is thought to undergo a tautomeric change, by which a colored substance with a quinone ring is formed.

One of the facts which is a necessary consequence of the mass law is, that if a base is added to a solution containing two acids, it (in effect) neutralizes the stronger one of the two or the one furnishing the larger number of ions. In a titration of an acid with a base in the presence of phenolphthalein, we have the presence of an acid in the indicator itself. It is present in

very small amounts, however, and furnishes very few hydrogen ions, so that it does not begin to be neutralized until practically all of the stronger and more highly concentrated acid is used up. When this point is reached the phenolphthalein, which is a diphenol, is neutralized to some extent, and the resulting sodium salt undergoes rearrangement to the colored form, by a breaking of the five-membered ring, and a shifting of the valences. The rapid breaking and reforming of this lactone ring on the addition of alkali and acid respectively is worthy of note.



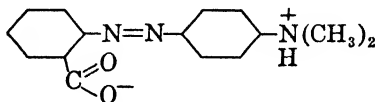
Methyl orange is an indicator which has been extensively used because it is not sensitive to weak acids such as carbonic acid and hence can be used as an indicator in the titration of strong acids directly against carbonates. Methyl orange, however, does not change color as abruptly as some other indicators, and for this reason has been discarded by some chemists. It is used in the form of a sodium salt, with the structure:



In alkaline and faintly acid solutions, the solution is yellow, and changes to red on the addition of an acid. The reason for the change in color is not well understood. It will be noted that the indicator is the salt of a rather strong acid and as such, even in the great dilution in which it is present in a titration, would not

be converted into the inner salt form except by the presence of a *comparatively* high concentration of acid. The change in color probably takes place at the same time that this is formed. The inner salt is a beautiful violet-colored crystalline compound known as *helianthin*.

Methyl red is a substance with the structure:



Methyl red

It is faintly yellow in alkaline (and very slightly acid) solutions and red in acid solution. The complete change from yellow to red requires the addition of a considerable amount of acid, but at a certain point only an extremely small amount of acid is necessary to bring about a distinct change of tint. At this point, the addition of about .01 ml. of .1 *N* acid to 25 ml. of solution produces a very appreciable intensification of color. Methyl red like methyl orange is sensitive to weak bases and not sensitive to weak acids. It is especially useful in titration of ammonia as in the Kjeldahl method. Many other indicators are used for titrations and for colorimetric determination of hydrogen ion concentrations, especially in biological work, but space will not permit their discussion.

PROBLEMS

1. Why are no bromine or iodine compounds listed among the most important intermediates?
2. The government reports show that the amount of aniline produced in U. S. in 1938 was 26,750,000 lbs. How much nitrobenzene would be necessary to prepare this amount of aniline? Compare this with the amount of nitrobenzene actually produced.
3. Work out the formulas of azo dyes which might be made from (a) *p*-nitroaniline and phenol, (b) from sulfanilic acid and dimethylaniline, (c) anthranilic acid and dimethylaniline. Compare the formulas obtained in (b) and (c) with those of methyl red and methyl orange.
4. How much sulfanilic acid with one molecule of water of crystallization would theoretically be necessary to manufacture 1,128,000 lbs. of

Orange II? Would you infer from this and the production figures (1938) given that sulfanilic acid is used in the manufacture of important dyes, other than Orange II?

5. Suppose that you add very slowly to a strongly basic solution an excess of a dilute solution of a strong acid. Arrange the indicators, litmus, phenolphthalein and methyl red, in the order in which they would be affected if present. The actual amount of difference, in case both the acid and base are strong, would be very slight.

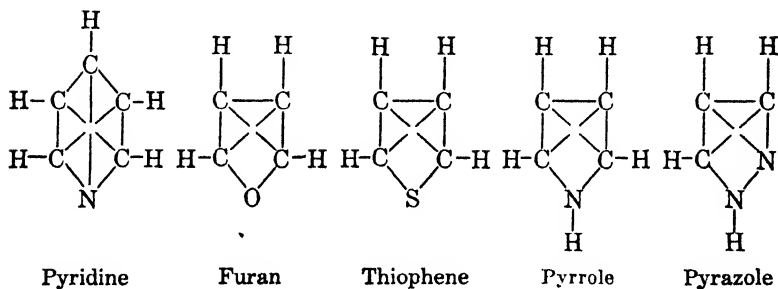
6. The dye known as Bismark Brown is made by treating *m*-phenylenediamine with two equivalents of nitrous acid and coupling twice with *m*-phenylenediamine. Write the structural formula.

CHAPTER XXXVI

HETEROCYCLIC AROMATIC COMPOUNDS

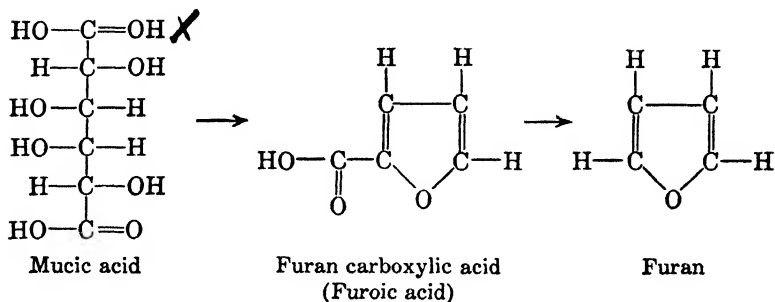
Furan, Thiophene, Pyrrole, Pyrazole

The aromatic compounds which we have considered so far have been aromatic hydrocarbons and their derivatives, or compounds in which a stable ring of carbon atoms is present. Such substances as phthalic anhydride contain a heterocyclic ring but the heterocyclic rings with which we have been concerned have been mainly unstable rings. We have now to consider compounds which have a stable heterocyclic nucleus. The substances with the formulas given below are the most important representatives of this type.

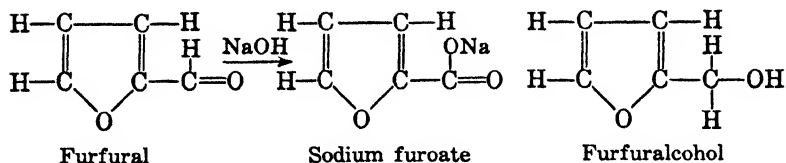


The evidence upon which these formulas are based will not be given in detail. *Pyridine*, C_5H_5N , for example, is represented as ring compound because in many respects it closely resembles benzene. It forms substitution products analogous to those of benzene, and these are able to go through various transformations without altering the nucleus of five carbon atoms and one nitrogen atom. In fact all of the substances represented by the above formulas form *substitution* products, and show a similarity to benzene, in that the ring of atoms does not easily break. It is for this reason that they are here represented by the centric formulas; it calls attention to their "aromatic" character.

Furan, C_4H_4O , itself is not of great importance. When *mucic acid*, the dicarboxylic acid derived from galactose, is heated, it loses carbon dioxide and water, probably after the manner indicated below, and forms *furan carboxylic acid*. This substance resembles benzoic acid in properties, and from it, by distillation of its barium salt with soda lime, furan may be prepared.



Furfural (furfuraldehyde) is the most important derivative of furan, and has already been mentioned as a product of the action of acids on pentose sugars (p. 353). It also occurs in the products of wood distillation. It resembles benzaldehyde in some of its properties, especially in that treatment with strong alkali produces the corresponding acid and alcohol by intermolecular oxidation and reduction.



Furfural has recently grown to be a substance of considerable industrial importance in the manufacture of resinoids similar to Bakelite (p. 99) and as a selective solvent in the refining of petroleum oils.

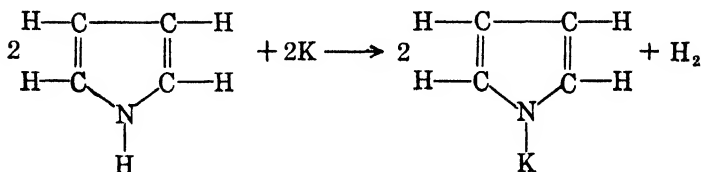
Thiophene, C_4H_4S , is present in the benzene obtained from coal tar unless extra precautions are taken to remove it. Its boiling point is 84° . This is only 3.5° higher than that of benzene

so it is not practicable to separate them completely by fractional distillation. The homologs of thiophene are also present in coal tar and are likely to contaminate the homologs of benzene which are obtained from this source. The correspondence between the boiling points of the two types of substances is shown below.

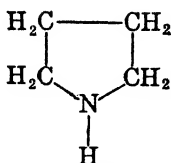
	B. P.		B. P.
Benzene, C_6H_6	80.5°	Thiophene, C_4H_4S	84°
Toluene, $C_6H_5CH_3$	110.3°	2-Methyl thiophene, $C_4H_3SCH_3$	113°
p-Xylene, $C_6H_4(CH_3)_2$	138°	2, 5-Dimethyl thiophene, $C_4H_2S(CH_3)_2$	137°

Thiophene yields nitro derivatives and sulfonic acid on treatment with nitric and sulfuric acids respectively, and thus shows its aromatic character. Many other derivatives are known. The two methyl thiophenes are converted by oxidation into two corresponding carboxylic acids. The three possible dicarboxylic acids are known.

Pyrrole, C_4H_5N , is present in coal tar and in bone oil. The latter is made by dry distillation of bones for the production of bone charcoal for decolorizing purposes. As indicated by its formula, pyrrole is a secondary amine, and as such forms salts with acids. Its base-forming property is very weak, however, due to the influence of the ring and its unsatisfied valences (p. 448). It has weak acidic properties, however, and reacts with metallic potassium, liberating hydrogen.

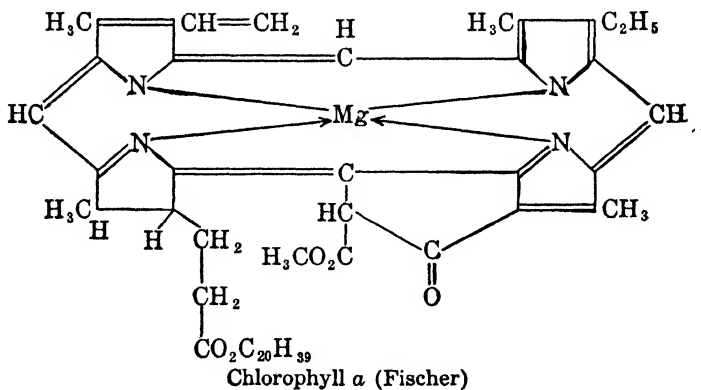


Homologs of pyrrole are known and on oxidation they produce pyrrole carboxylic acids. A large number of substitution products of pyrrole are known in which the nucleus of four carbon atoms and one nitrogen atom is present, but they are not of particular importance. Pyrrole can be reduced to a saturated substance called *pyrrolidine* to which is ascribed the formula:

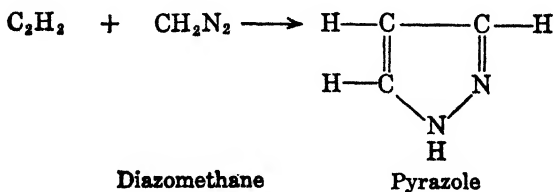


Pyrrolidine

Chlorophyll, which is one of the active agents in photosynthesis, consists of two closely related substances called *chlorophyll a* and *chlorophyll b*; the former occurs in larger amount in leaves. Their complete structures have not been determined with certainty though there are only a few points about which there is difference of opinion. The presence of coordinate valences to the magnesium explains its failure to be removed by hydrolysis. (Magnesium nitride or amide is very reactive with water.) The presence of pyrrole nuclei in the formula is to be noted.

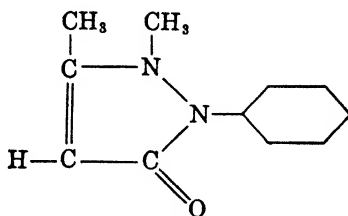


Pyrazole. This is a synthetic compound which shows typical aromatic behavior. It may be prepared from acetylene and diazomethane (p. 217).



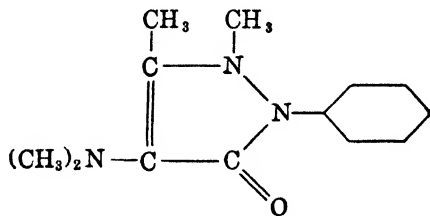
It may be nitrated and sulfonated though less easily than benzene, and amino pyrazole can be diazotized and coupled like aniline. Pyrazole like pyrrole is a secondary amine. It is also a tertiary amine.

Antipyrine is a derivative of pyrazole which is used in medicine to combat fever. Its structure is indicated below. It should be noted that it does not contain an unchanged pyrazole ring.



Antipyrine

Pyramidone is another pyrazole derivative which is used extensively as an analgesic especially in conjunction with amytal (p. 254), which tends to induce sleep.



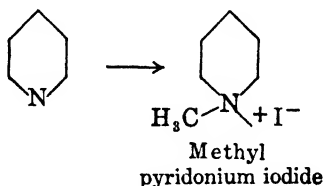
Pyramidone

Pyridine and Its Derivatives

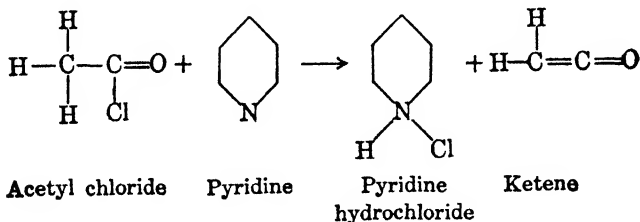
Pyridine, C_5H_5N , is a disagreeable smelling compound which is found in coal tar, also in bone oil. It boils at 115° , is miscible with water in all proportions and is an excellent solvent for many organic as well as inorganic substances. In most respects pyridine is a very stable substance; it is exceedingly stable toward oxidation and does not form derivatives on heating with nitric acid except under extreme conditions. It is slowly attacked by

sulfuric acid to form a sulfonic acid and by bromine to form bromine substitution products.

Addition Reactions. Pyridine is, however, a tertiary amine and forms salts readily. In this respect, of course, it shows a striking contrast to benzene. That it is a tertiary amine is shown by the fact that it forms salts by reaction with acids, but does not react with nitrous acid. If pyridine is treated with methyl iodide, an addition reaction takes place.

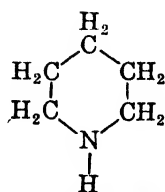


The readiness with which this and other similar reactions take place is striking. There is a strong tendency for the nitrogen atom to increase its valence. This is illustrated by the fact that pyridine will abstract the elements of hydrochloric acid from compounds, as, for example, from acetyl chloride.



The ketene indicated in this equation does not pass off as such, but undergoes polymerization or condensation of some kind. Pyridine is often used as a solvent in which an acetylation is carried on. The alcohol or phenol may be dissolved in pyridine and acetyl chloride or acetic anhydride added to the mixture. The pyridine probably converts the acetyl chloride into ketene which reacts by addition with the alcohol (p. 137).

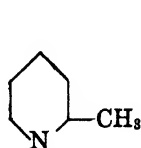
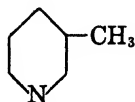
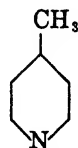
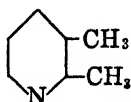
Reduction. Pyridine can be reduced by the action of hydrogen liberated from water or alcohol by sodium, forming hexahydropyridine or *piperidine*.



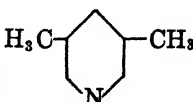
Piperidine

This substance can be obtained from black pepper, by extraction with alcohol and hydrolysis of the products. Piperidine is one of the products of hydrolysis of a more complex substance present in the pepper, known as *piperine*, $C_{17}H_{19}NO_3$ (p. 589). Piperidine, as would be expected from the formula ascribed to it, acts as a secondary amine; with nitrous acid it forms a nitrosoamine.

Derivatives of pyridine are numerous. There are three homologs of pyridine with the formula $CH_3C_5H_4N$, known as *picolines*, and six dimethyl pyridines known as *lutidines*. These substances resemble pyridine in most properties. They undergo oxidation to form the corresponding carboxylic acids which is analogous to the behavior of toluene and the xylenes. The acids, like those derived from benzene, can be distilled with lime to produce the parent substance pyridine. The monosubstitution products are designated by the Greek letters α , β or γ , depending on the position, and the positions occupied in di- and tri-substitution products are designated by numbers as illustrated below.

 α -Picoline β -Picoline γ -Picoline

2, 3-Lutidine

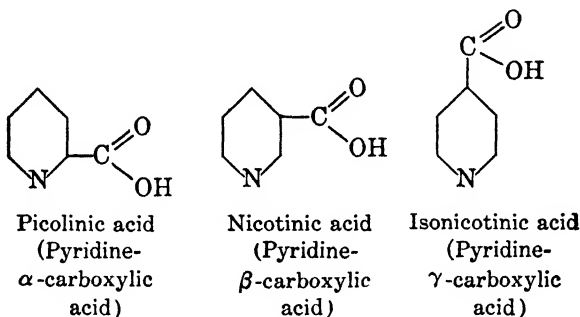


3, 5-Lutidine

Hydroxypyridines can be made by fusing sulfonic acids with alkali, and thus in their method of preparation resemble phenols.

Aminopyridines can be produced by reduction of nitropyridines, and like the other aromatic amines these substances can be diazotized and the resulting compounds coupled with phenols and anilines.

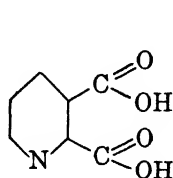
The **pyridine carboxylic acids** are of some particular interest since they are formed by the oxidation of alkaloids, which are to be discussed in the next chapter. The formulas of the mono-carboxylic acids are given below.



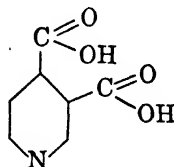
These are all crystalline substances soluble in water, and may, like the amino acids, form salts with either acids or bases. They exist in solution as inner salts. *Nicotinic acid* gets its name from the fact that it was first obtained by the oxidation of the alkaloid *nicotine*. The amide of nicotinic acid is an important constituent of enzyme systems in the body and the lack of sufficient amide (or the acid) in the diet results in pellagra (p. 603). The α -pyridine carboxylic acids lose carbon dioxide easily on heating and show a contrast to the β and γ acids in this respect. They also give a characteristic reddish coloration with ferrous sulfate.

Quinolinic and cinchomeronic acids are thought to have the formulas given below based partially upon the following evidence. Both are di-acids and on distillation with lime produce pyridine. Both acids form anhydrides analogous to phthalic anhydride and the carboxyl groups are therefore in adjacent positions. In the case of quinolinic acid *one* of the carboxyl

groups is easily eliminated by heating and this is reason for believing that this carboxyl group is adjacent to the nitrogen.



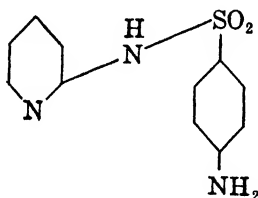
Quinolinic acid



Cinchomeronic acid

Our principal interest in these acids lies in the fact that they may be obtained from various alkaloids by oxidation, and thus they throw light on the structure of the alkaloids.

Sulfapyridine with the formula indicated below is a highly important medicinal (p. 452) which is valuable in numerous diseases due to bacterial infection, including pneumonia.

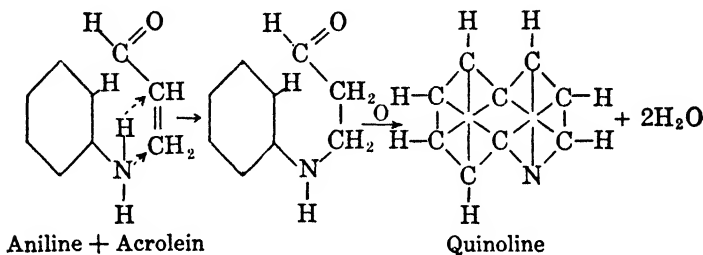


Quinoline, Isoquinoline, Etc.

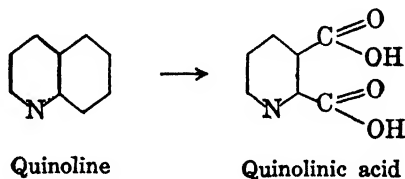
Quinoline, C_9H_7N , has been obtained from bone oil and is also related to, and may be obtained from, certain alkaloids such as quinine. It may be synthesized rather readily from aniline and acrolein, and nitrobenzene. The nitrobenzene acts only as a mild oxidizing agent, and the acrolein is ordinarily made in the same solution in which the synthesis takes place by the action of sulfuric acid on glycerol. The reaction is known as *Skraup's synthesis*, and in accordance with experimental evidence is thought to take place in the manner indicated below. The fact

¹ Z. H. Skraup (1850-1910) was Professor of Chemistry in the University of Vienna.

that quinoline is made from aniline indicates that it has a benzene ring in its structure, and since pyridine can be obtained from quinoline, it seems reasonable that it also contains a pyridine ring as demanded by this interpretation of the synthesis.



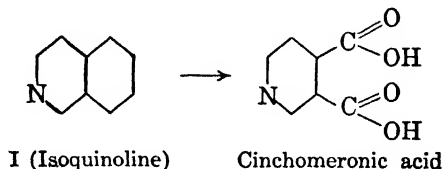
In accordance with the structure given above quinoline solutions are alkaline and it is able to form salts with acids by addition. It does not react with nitrous acid and must therefore be a tertiary amine. It does add on methyl iodide, and in other reactions of this type is very much like pyridine. We have already noted that pyridine is more stable toward oxidation than benzene, and in accord with this fact, oxidation of quinoline destroys principally the benzene ring and forms quinolinic acid. The pyridine ring is also broken to some extent forming phthalic acid.



This fact, in addition to its method of synthesis, establishes the formula of quinoline so far as arrangement of atoms is concerned. Direct nitration or sulfonation of quinoline forms products in which the substituents are on the benzene nucleus. Substitution products in which the substituents are attached to the pyridine nucleus are, like the corresponding pyridine derivatives, difficult to form.

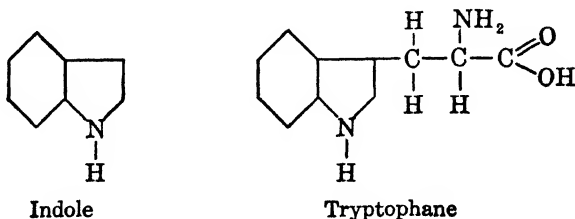
There are seven possible methyl quinolines and all are known. In addition a great many other derivatives have been prepared. Derivatives of quinoline are obtained from some of the alkaloids.

Isoquinoline occurs with quinoline in bone oil, and as the name indicates it is isomeric with quinoline. The structure of isoquinoline (which is very similar to quinoline in chemical properties) is easily established from the fact that on oxidation cinchomeronic acid (in addition to phthalic acid) is formed.



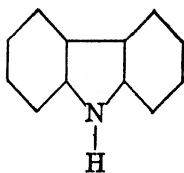
This could not happen unless isoquinoline has the structure represented by formula I. Isoquinoline, like quinoline, is related to certain alkaloids.

Indole has in its structure a benzene and a pyrrole ring. It has, in the crude state, a disagreeable odor but when pure is used in perfumery. It is formed by bacterial action on proteins. *Tryptophane*, an amino acid obtained from proteins, has the indole nucleus in its structure.

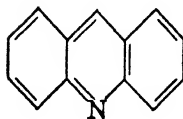


A reference to the structure of indigo (p. 567) will show that there are two indole rings in its structure.

Carbazole, $C_{12}H_9N$, which occurs abundantly in coal tar and which is used for making certain dyes, consists of an indole nucleus condensed with a benzene nucleus, as indicated. It is a very stable substance.



Carbazole



Acridine

Acridine, $C_{13}H_9N$, which has the structure indicated above, occurs in coal tar. Several important dyes are derivatives of it.

PROBLEMS

1. What chemical test could be used to differentiate pyridine and pyrrole?

2. Furan might be considered as a type of inner ether. On this basis would the ring be expected to be more or less stable than the ring present in succinic anhydride?

3. What could be stated concerning the structure of nicotine from the fact that nicotinic acid is produced from it by oxidation?

4. Would you expect pyridine derivatives to be easy or difficult to digest in the Kjeldahl method for determining nitrogen? (p. 314).

5. How many mono-substitution products of isoquinoline would be possible? How many di-substitution products of quinoline would be possible provided that both substituents are the same?

6. How many homologs of pyrrole would be possible, having the molecular formula C_6H_8N ?

7. One gram of furfural is treated with 1 ml. of 10 *N* sodium hydroxide solution, and after the reaction 4.8 ml. of normal acid is required to neutralize the excess alkali. What would be the value obtained for the molecular weight of the furfural, assuming that the reaction goes as indicated in the text?

8. Carbazole reacts with potassium hydroxide and forms a potassium derivative in which a hydrogen atom is replaced. Which of the nine hydrogen atoms would you expect to be replaced? Why?

9. Write the formula for the nitrosoamine derived from piperidine.

CHAPTER XXXVII

ALKALOIDS

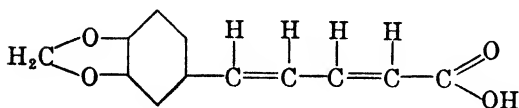
Certain types of basic substances which are obtained from vegetable sources are called *alkaloids*.¹ The name suggests their alkaline character. Though basic amino acids, basic proteins, and purine bases, etc., are obtainable from plants, they are not ordinarily included among the alkaloids. The alkaloids usually have distinct physiological action and may be used for medicinal purposes. They are sometimes termed the "active principles" of certain plants. The alkaloids which are well recognized and have been studied extensively are for the most part, derivatives of pyridine, quinoline, or isoquinoline. However, it would not be wise to include this relationship in a definition of alkaloids since some of the typical alkaloids are not derived from any of these substances. An example of an alkaloid which is not a derivative of any of these substances is *ephedrine*, $\text{C}_6\text{H}_5\text{CHOHCH}(\text{NH}-\text{CH}_3)\text{CH}_3$, which was first obtained from an evergreen shrub and is used extensively in medicine.

Most of the alkaloids are solids at ordinary temperature, but nicotine, a liquid, is an exception. They are generally only slightly soluble in water but dissolve in dilute mineral acids because they are basic and form soluble salts. The free alkaloids are generally soluble in alcohol. The alkaloids are precipitated from the solution of their salts by tannic acids, phosphotungstic acid, phosphomolybdic acid, picric acid, chloroplatinic acid, the double salt, potassium mercuric iodide, etc. In most of these cases the precipitation is due to the formation of insoluble salts. These same reagents may be used for the precipitation of proteins or other complex substances of basic nature. They are spoken of frequently as *alkaloidal reagents*.

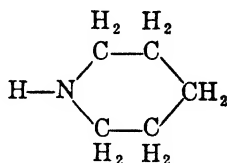
¹ For fuller treatment than is given here see Chapter 15 (L. Small) Gilman, *Organic Chemistry, An Advanced Treatise*. (Second Edition.)

Pyridine Alkaloids

Piperine, $C_{17}H_{19}NO_3$, has already been mentioned (p. 582) in the discussion of piperidine. It is present in pepper, and on hydrolysis, which takes place in the presence of either acids or bases, *piperic acid* and piperidine are produced.

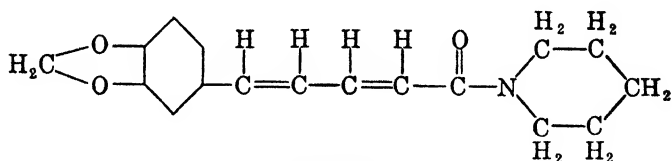


Piperic acid



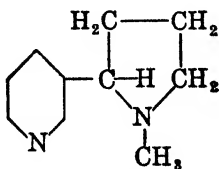
Piperidine

Piperic acid can be converted into an acid chloride which reacts with piperidine to form piperine. This reaction and other relationships show that piperine is a substituted amide of the structure given below. The linkage is thus similar to that present in proteins.



Piperine

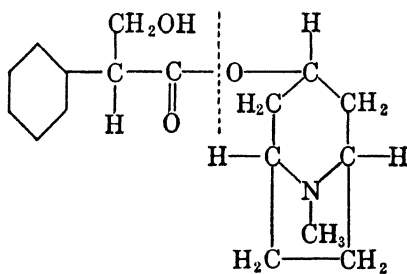
Nicotine is the principal alkaloid present in tobacco leaves, in which it is present as the nicotine salts of malic and citric acids. The fact that nicotine forms nicotinic acid on oxidation has already been mentioned. It has been synthesized and proved to have the structure:



Nicotine

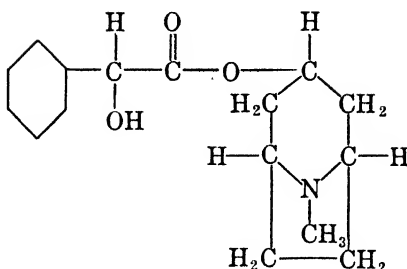
The reduced pyrrole ring present in its structure is broken on oxidation. In accordance with this formula, which contains an asymmetric carbon atom, there are *dextro* and *levo* forms of nicotine. The synthetic product is of course inactive, but can be resolved into the two optically active forms. The naturally occurring form, as in the case of most of the alkaloids, is *levorotatory*. This form is a much stronger poison than the *dextro* form which may be separated from the synthetic product.

Atropine is obtained from the deadly nightshade (*Atropa belladonna*) along with other alkaloids. It has been used in medicine to dilate the pupil of the eye, but for this purpose has been largely replaced by *homatropine*, a related substance. The following structure has been assigned to atropine.



Atropine

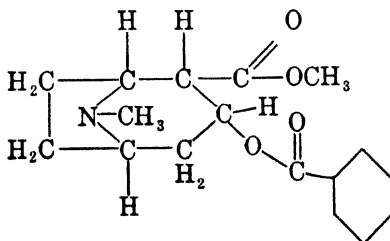
In this formula there is a benzene ring, a reduced pyridine ring and a reduced pyrrole ring. The last is pictured in such a way as to make it not readily recognizable. The dotted line drawn through the formula is to call attention to the fact that the substance, as formulated, is an ester. The acid is called *tropic acid* or *atropic acid* and the complex alcohol is called *tropine*. The *mandelic acid* ester of tropine is prepared synthetically and is known as *homatropine*. It dilates the pupil of the eye more rapidly than atropine and a normal condition returns more quickly after its use, so it has distinct advantages though the use of atropine for children has not been outmoded.



Homatropine

The structures of these substances are mentioned, not because they are of such outstanding importance, but because they illustrate facts which are to be discussed shortly.

Cocaine (kō'kâ-in) is present in the leaves of the cocoa plant, a South American shrub. It has been used as a local anesthetic but is now largely replaced by novocaine (p. 508) and other synthetic products. Like atropine it is an ester, in fact a di-ester, as it yields on hydrolysis methyl alcohol; *ecgonine*, an alcohol-acid, and benzoic acid. Its structure is indicated below.

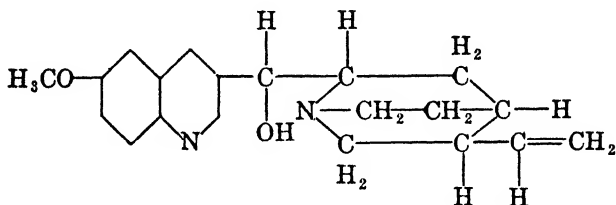


Cocaine

Quinoline Alkaloids

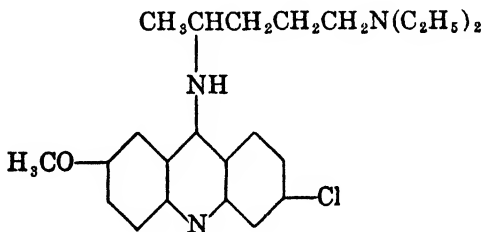
Quinine is perhaps the most important of all alkaloids because of its use as an antimalarial. It is found in the bark of different varieties of cinchona trees which are indigenous to South America, however, the main source of quinine in recent years has been from plantations in the Dutch East Indies. It is present, along with many other alkaloids, combined with quinic

acid (a derivative of hexahydrobenzene, $C_6H_7(OH)_4-COOH$), or with complex tannic acids. The shortage of quinine during World War II led to extensive research directed toward its synthesis and toward the discovery and production of other and better antimalarials. The total synthesis of quinine has been achieved (Woodward, 1944).



Quinine

More than 15,000 compounds were tested during this research and several show promise of being able to replace atebirin, the only antimalarial used clinically during the war as a substitute for quinine.



Atebrin

Cinchonine occurs with quinine in cinchona bark, and is similar to quinine in medicinal properties but is physiologically less active. It is closely related structurally to quinine, differing only in that the methoxy group is absent.

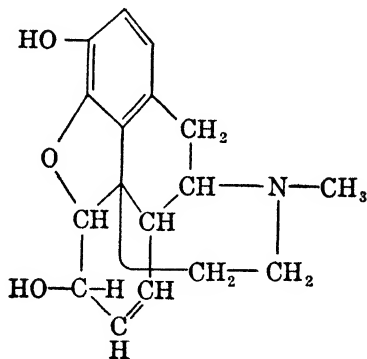
Strychnine occurs along with *brucine* in *nux vomica*, the seed of an Asiatic tree. It is very poisonous and is used for the extermination of rodents, etc. It is also given in very small doses in medicine, as a tonic and as a heart stimulant. The molecular formula is $C_{21}H_{22}O_2N_2$, but the structure is not fully known. It

yields quinoline and indole on fusion with potassium hydroxide, and may also be made to yield carbazole.

Brucine is similar to strychnine in properties. Structurally it differs only in the presence of two methoxy groups which are absent in strychnine. It is less poisonous and less important than strychnine.

Opium Alkaloids

Opium is the dried juice from unripe seed capsules of certain varieties of poppy. It contains a large number of alkaloids of which over twenty have been isolated. The one which is present in greatest amount is morphine, which constitutes about 10 per cent of the opium, and which is responsible for a large part of the physiological action of the opium. Its accepted structure is indicated below:



Morphine

On distillation with zinc dust it yields phenanthrene. It contains two hydroxy groups one of which is a phenolic group. Evidence for this is based upon the fact that morphine unlike other alkaloids is soluble in a sodium hydroxide solution, but is insoluble after it is methylated (converted into a methyl ether). Morphine may be oxidized to a ketone and hence has one secondary alcohol group. With acetic anhydride it forms a diacetyl product which is important in medicine and is known as heroin (hĕr'ō-in). The

methyl ether of morphine is known as codeine (kō'dé-ēn) and is also an important drug.

Relation between Constitution and Physiological Action.

We cannot enter into an extended discussion of the relation between the structure of the alkaloids and the synthetic products derived from them, and their physiological action. In our study of organic compounds we have noted that the formula indicates the chemical character of the compound; it is thus possible in very many cases to predict how a compound will act chemically under given conditions if we know its formula. In the case of more complex compounds, however, we find often that the formula is able, only in a rough way, to describe the behavior of the compound, and that unexpected reactions occur. When we deal with the question of physiological action the situation is even more complex. As has already been pointed out, knowledge of physiological action depends as much upon the knowledge of the chemistry of physiology as it does upon the knowledge of the chemistry of the drug in question. It would be very surprising, therefore, if we were able to predict physiological activity accurately from the formula of the substance, when we are not even able accurately to predict chemical behavior.

The fact remains, however, that substances with similar chemical constitution generally resemble each other in physiological characteristics. This is illustrated in the resemblance both in chemical structure and physiological action between atropine and homatropine; between quinine and cinchonine; between strychnine and brucine; and between cocaine and some of the related compounds which are used for a similar purpose. A study of the properties of many alkaloids and their derivatives makes it possible to predict with some success the properties of an unknown compound of the same general character. It is not possible, however, to ascribe definite physiological actions to definite chemical groups, in the same way that it is possible to correlate chemical action with definite groups. In the complete formula for morphine, we cannot point out the groups which are responsible for its peculiar effects. This is emphasized by the fact that its effects, as well as those of other drugs, are sometimes markedly different on different individuals.

PROBLEMS

1. Suppose you had a synthetic *dl*-mixture of two forms of an alkaloid. How could naturally occurring tartaric acid be used to resolve the mixture?

2. Why does not nicotine on oxidation produce a pyrrole carboxylic acid?

3. From the information given in the text (p. 591) write the formula for eegonine.

4. In what positions would you expect piperic acid to add on two atoms of hydrogen?

5. An alkaloid with one atom of nitrogen in the molecule forms a crystalline sulfate containing one molecule of water of crystallization. One gram of this sulfate on precipitation with barium chloride produces .338 g. of barium sulfate. What is the molecular weight of the alkaloid?

6. Is the molecular formula of strychnine such that it could have in its structure independent quinoline, indole and carbazole residues? How could the formation of these three substances from strychnine be explained?

CHAPTER XXXVIII

ORGANIC SUBSTANCES OF SPECIAL BIOCHEMICAL INTEREST

When it became apparent that carbon compounds could be produced in the laboratory independent of the action of organisms, and when the structure theory had been formulated as a working hypothesis, synthetic organic chemistry developed with unprecedented success. Chemists worked for the joy of creating substances which had never existed on this planet previously, and for the satisfaction obtained from the confirmation of the structure theory. This period was one of the most remarkable in the history of chemistry and in the history of any science.

Many of the outstanding chemists of this period, however, applied their skill to the chemical study of the natural products of the organic world: acids, sugars, proteins, alkaloids, pigments, etc. These substances in many cases were synthesized in the laboratory and brought under the "spell" of organic chemists.

Simultaneously, especially with the rise of the coal tar dye industry, the development of technical organic chemistry took place and at the present time the number of organic products and ways in which they are applied is stupendous and rapidly growing. All of the time especially with the rise of physical chemistry there has been developed a keener insight into the fundamentals of just how molecules are constructed and how they react.

With the increased knowledge of the vitamins, hormones and other "principles" which are present in tissues in minute but none the less important amounts, the organic chemist has been called upon again to unravel the problem of the structure of natural occurring organic substances—a problem which has always been close to the center of his interest. We shall take some space at this point to give the results of the extensive work which has resulted in the solution, or at least in great progress toward the solution, of several of these problems. These involve

substances of miscellaneous nature which do not fit naturally in our treatment at any other point.

It should be made clear here and stressed, that the discovery of the existence of these substances and their concentration and purification depends upon the development of biological tests for the entities concerned, and that without these tests the organic chemist with his usual equipment would generally be helpless. The situation is quite different from that which existed when the organic chemist was surrounded with natural products many of them readily crystallizable, and offering themselves for direct study. The products here mentioned have in general been sought out and singled out from a mass of inert material—an undertaking in some cases quite overshadowing the more straightforward but by no means simple task of determining structure.

Significance of Vitamins and Hormones. Our discussion will here be concerned in the main with two different groups of compounds, namely *vitamins* and *hormones*. The functioning of these substances is not properly discussed here, but general statements regarding them can well be made. Both vitamins and hormones are organic compounds which occur in the body in small amounts, and have peculiar (often indispensable) functions. In many cases the functions appear, superficially at least, to be of a catalytic nature.

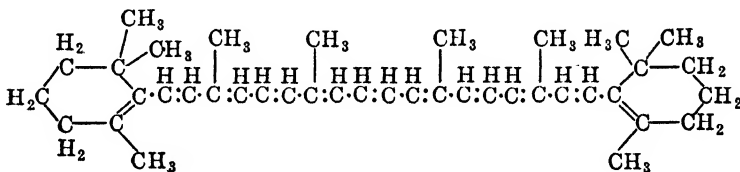
A fundamental distinction between vitamins and hormones is that hormones are synthesized by the body, whereas vitamins cannot be built up but must be furnished in the food. The terms *vitamin* and *hormone* are based upon physiological concepts and do not necessarily refer to specific substances. Thus any substance which will cause normal bone deposition and cure the condition of rickets may be referred to as "vitamin D." There is no single chemical substance, however, which can properly be called "vitamin D," since a number of compounds can perform this function. In our presentation we shall treat specific compounds primarily, and not physiological functions.

It should be pointed out that "vitamins" have no chemical characteristics in common and neither do the "hormones." Represented among the vitamins and hormones are compounds of

wide variety in composition and structure. Vitamins are, so far as they are known, relatively simple (non-colloidal) whereas hormones may be simple or may have the complexity of proteins.

Fat Soluble Compounds Possessing Vitamin Activity

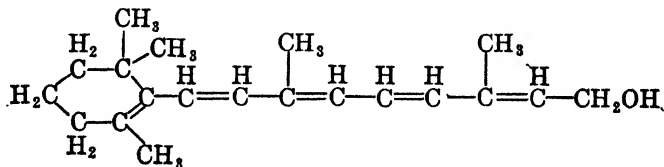
Carotenes and Carotenol. The pigment of carrots has long been recognized as a hydrocarbon, $C_{40}H_{56}$, and its occurrence in leaves has also been a familiar fact. Coincident with the discovery that this supposedly pure hydrocarbon can supply in experimental animals the need for vitamin A, new interest in its chemistry has developed. It is now known that not one but probably as many as four carotenes (α , β , γ and δ) are present in plant pigments. β -Carotene is represented below.



β Carotene (Karrer)

The extreme unsaturation of the molecule (11 double bonds) and the presence of repeating isoprene skeletons (p. 57) should be noted.

If β -carotene is taken in the food it is transformed in the liver into two molecules of carotenol (vitamin A), a nearly colorless substance. It has the structure given below.

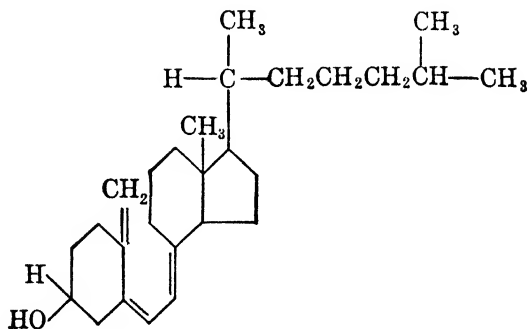


Carotenol (vitamin A) (Karrer)

Vitamin A and carotene are interchangeable in the diet. The vitamin A content of foods (butter, for example) cannot be

judged from the color since both carotene and carotenol may be present. Life and growth of higher animals are impossible without vitamin A. It functions in various tissues but its effects are particularly notable in epithelial tissues. It enters into the composition of the complex material "visual purple." The next higher homolog of carotenol, homocarotenol, occurs in the livers of fresh-water fish and also functions as "vitamin A." Esters of both alcohols also occur naturally and are physiologically active.

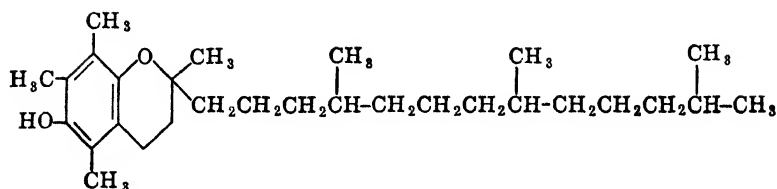
Calciferols and Related Compounds. Research in recent years has shown that there are a number of closely related sterols either occurring naturally or produced by irradiation, etc., of other sterols, which are anti-rachitic or possess vitamin D activity. The chemistry of these compounds is complex. Certainly one of the most important naturally occurring "vitamins D" is "vitamin D₃" derived by irradiation from 7-dehydrocholesterol.



Vitamin D₃*

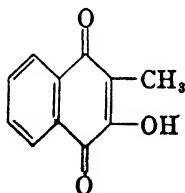
Tocopherols. Sterility can be developed in animals by dietary means, and the condition can be cured or prevented by "vitamin E." Two naturally occurring substances with closely related structures (α and β tocopherol) possess "vitamin E" activity. The structure of α tocopherol is

* In the formulas for steroids (sterols and closely related compounds) hexagons are often conveniently used to represent cyclohexane instead of benzene rings. The student must be on his guard and interpret abbreviated formulas on the basis of the context.

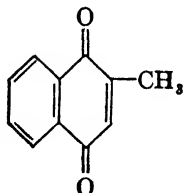
 α -Tocopherol

In addition some forty related synthetic compounds have appreciable (and variable) vitamin E activities.

Compounds Possessing "Vitamin K" Activity. A condition involving a delayed clotting of the blood can be developed in chicks by excluding "vitamin K" from the diet. The experimental fowls can be brought back to normal in this regard by the administration of a number of related organic compounds among which phthiocol, 2-methyl-3-hydroxynaphthoquinone, and 2-methylnaphthoquinone are highly active.

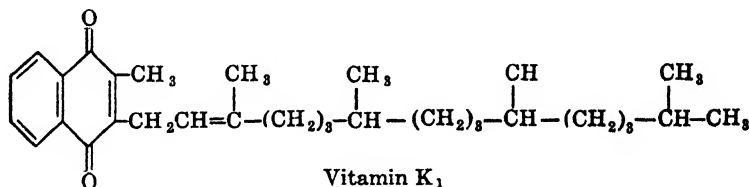


Phthiocol



2-Methylnaphthoquinone

More common naturally occurring vitamins K (K_1 and K_2) possess the same ring with a long side chain.

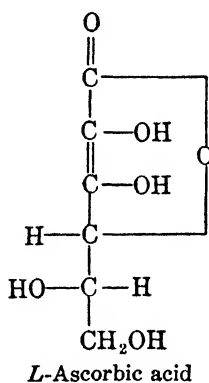
Vitamin K_1

One synthetic compound has been produced which possesses appreciable vitamin E and vitamin K activity.

Ascorbic Acid (Vitamin C)

That fruit juices and fresh foods contain something which prevents scurvy has been suspected or at least indicated for centuries. Within recent decades the active material has been isolated in the form of a single crystalline substance, which was synthesized in 1933. It occurs widely in nature but unlike the compounds to be discussed later in this chapter it appears not to be essential to all forms of life, since bacteria and yeasts, for example, appear to live entirely in its absence and without producing it. Higher animals, such as rats, which do not require it in the diet (and as a result do not suffer from scurvy), produce it readily within their bodies.

The structure of ascorbic acid which relates it to the sugars (L glucose) follows:



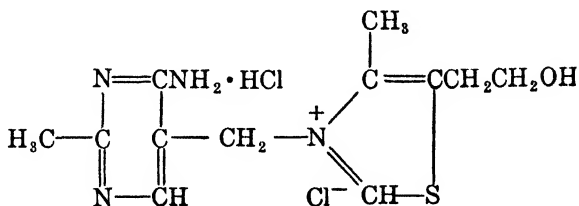
It is a very easily oxidized substance and can be determined by carefully controlled reduction methods. It is the most abundant (in terms of actual weight) of the known vitamins. Certain plant sources (paprika, iris leaves) contain as much as 0.3 per cent and certain species of gooseberries are said to contain as much as 2 per cent ascorbic acid. Larger amounts are required in the diet than in the case of the other vitamins so that diets may be deficient in this respect despite the relative abundance in nature. The largest single use of ascorbic acid as a pure chemical is not, however, as a vitamin but as an antioxidant (p. 393) to

prevent discoloration (darkening) of quick-frozen light fruit upon defrosting.

B Vitamins

Investigations in recent years have led to the recognition of two types of vitamins: (1) those which function only in highly specialized organisms, and (2) those which are universal constituents of all living matter and make up part of the catalytic equipment in all living cells, whether plant, animal or bacterial. The vitamins discussed up to this point appear to belong to the first type, while the "B vitamins" to be discussed in the following paragraphs appear to be essential cogs in the machinery of all living matter.

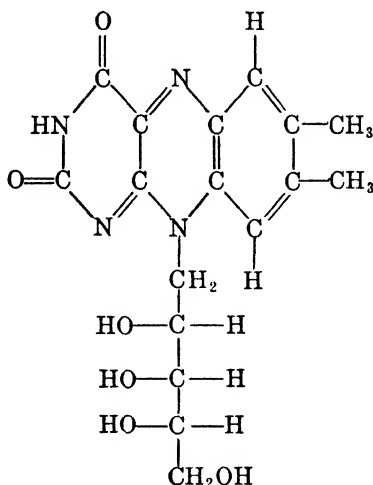
Thiamin. This substance enters into specific catalytic systems which are essential to life. In man and experimental animals its lack produces beri-beri or polyneuritis. Its chemical nature is interesting because it is a pyrimidine derivative (p. 330) and at the same time contains the *thiazole* nucleus which has not hitherto been encountered in this text. The fact that the compound is a quaternary ammonium salt should be noted.



Thiamin (R. R. Williams)

So far as is known, thiamin is the only natural substance possessing "vitamin B₁" activity.

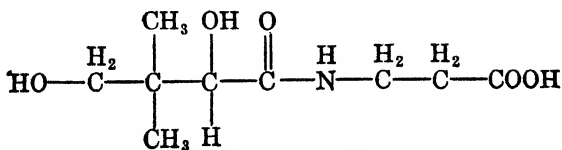
Riboflavin. This substance is the water soluble yellow pigment in milk (whey), and is an essential constituent of the diet of animals including human beings and functions in the catalytic systems of all organisms. The structure is given below. Its lack of chemical relationship to other vitamins should be noted. The sugar group is related to *ribose* from which the name is derived.



Riboflavin (Kuhn)

Nicotinamide. This compound has been known for many years but its "vitamin" properties have been recognized only in recent years. Nicotinic acid (p. 583) can replace it in the diet. In humans either of these two substances prevent pellagra. It enters into catalytic oxidation-reduction (enzyme) systems.

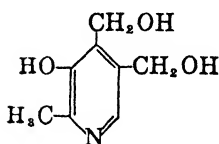
Pantothenic Acid. This acid was so named (Gr. *pantotheren*, from everywhere) because of its universal occurrence, and was the first B vitamin for which this observation was made. Unlike most of the vitamins discussed up to this point it was discovered and isolated not on the basis of animal experiments but by using yeasts and bacteria as test organisms. It is essential for all forms of life where it functions in catalytic systems. Higher animals are unable to produce it within their bodies but depend on plants for an ultimate source.



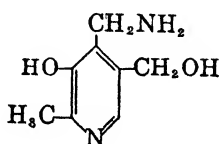
Pantothenic acid

It is a peptide-like compound and yields on splitting pantoic acid (which spontaneously lactonizes) and β -alanine, $\text{CH}_2\text{NH}_2\text{CH}_2\text{COOH}$.

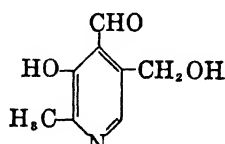
Pyridoxine, Pyridoxal and Pyridoxamine (B_6 group) are three closely related compounds which are often interconvertible in tissues and take part in a catalytic system of universal biological occurrence. Their structures contain the pyridine nucleus as their names suggest.



Pyridoxine

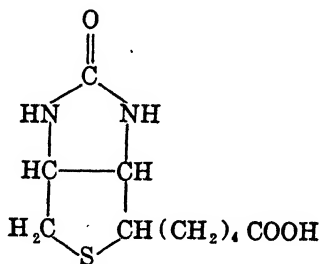


Pyridoxamine



Pyridoxal

Biotin. This substance like pantothenic acid was discovered because of its effect on yeast growth (Kögl), but is also necessary for animals and possesses the physiological activity originally ascribed to "vitamin H."



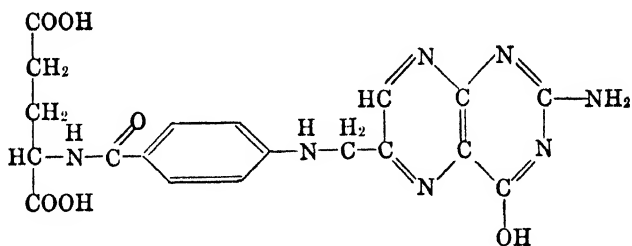
Biotin (du Vigneaud)

Egg white contains a specific protein *avidin* which combines with biotin and renders it not available. The vitamin properties of biotin were discovered in using diets containing large amounts of raw egg white. When animals are fed such diets they need to

be supplied with relatively large amounts of biotin. In the absence of raw egg white intestinal bacteria produce enough biotin to fill an animal's requirement. Avidin is inactivated by cooking.

***p*-Aminobenzoic acid** is another example of a compound which was known for many decades before its vitamin properties were suspected. Evidence, which is in some cases indirect, shows that this aromatic compound is an essential part of the catalytic machinery of all living cells. The discovery of the biological importance of *p*-aminobenzoic acid was dependent upon studies involving sulfanilamide (p. 453) and its antibacterial activity.

Folic Acid. This B vitamin was so named because leaves (Latin, *folium*, leaf) are good sources of it but not of the other B vitamins. It was discovered and obtained in highly concentrated condition using bacteria as test organisms. Its antianemic properties for chicks and for other animals were demonstrated later.



It may be noted that the folic acid molecule as written above consists of three portions: a glutamic acid residue on the left, a *p*-aminobenzoic acid residue, and a *pterin* residue on the right. The heterocyclic structure on the right is related to *xanthopterin*, a pigment originally found in the wings of butterflies.

It may be that *p*-aminobenzoic acid exists in tissues as a component of folic acid only and does not function as a vitamin, except as a part of folic acid.

Inositol. $C_6H_6(OH)_6$ previously mentioned (p. 399) is of undoubted biological importance and appears to occur universally in living matter. Its status as a "B vitamin" may be open to question because its potency as a biochemical factor is relatively low; the amount required to bring about a physiological effect is relatively large and its functioning as a component of a catalyst is not certain.

Choline which has already been mentioned (p. 333) is sometimes thought of as a B vitamin. Even though it is or may be of nutritional importance it does not fit well into the classification because it serves as a raw material used in biosynthesis rather than catalytically.

Antibiotics and Antimetabolites

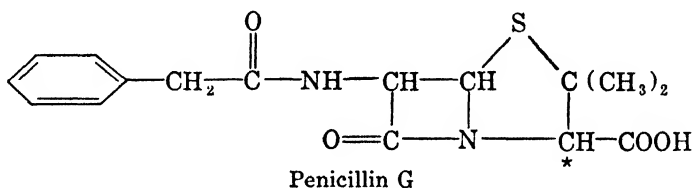
As an outgrowth of vitamin investigations and of the discovery of the sulfa drugs, a new era in the development of synthetic drugs for combating parasitic organisms has begun.

Numerous drugs of greater or lesser promise have been produced by synthesizing "imitation vitamins," substances which resemble actual vitamins in chemical structure but do not perform the functions. Such compounds may have the capability of entering into the structure of a specific catalytic system of an organism, and of thereby rendering it inert. The sulfa drugs, because of their structural resemblance to *p*-aminobenzoic acid, block the latter substance out of its functioning position in certain organisms and prevent the growth of the organism.

There is every reason to expect that in the future when fuller details regarding the catalytic systems and their functioning in various organisms are known, numerous highly effective drugs will be made to order on the basis of their ability to interfere with specific metabolic processes.

In the meantime, however, several natural-occurring antibiotic substances, which presumably function in a similar manner, have been found to be of very great value; outstanding

among these are *penicillin* and *streptomycin*. It would take us too far afield to discuss the chemistry of these and related compounds in any detail. Penicillin has been studied the most thoroughly to date. There are several penicillins, the most important of which is penicillin G with the structure:



The antibiotic potency of this compound resides in the fused ring portion of the molecule because various substitutions replacing the benzyl group (on the left) can be made without altering seriously the physiological properties of the compound. It is interesting and probably significant that the carbon atom marked with an asterisk has a configuration opposite to that of the amino acids which are derived from proteins.

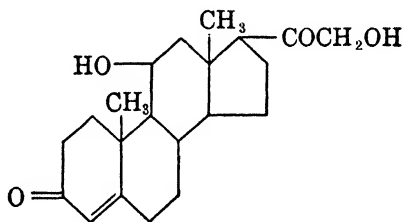
Organic Substances Possessing Hormone Activity

The simplest organic substance which possesses activity similar to that of a hormone is *carbon dioxide*. It is produced in the body by combustion, and an important function, among others, is to stimulate the nerve center of the brain which controls respiration. It is indispensable as an agent for inducing respiratory movements. Carbon dioxide is not regarded as a typical hormone because instead of being a specialized highly potent chemical produced by a particular tissue it is a common substance produced in relatively large amounts by all tissues. *Glucose*, *urica* and a number of other substances which may be produced in the body and which are physiologically important by virtue of their ability to be carried in the blood to a specific organ have some of the characteristics of hormones, but again are not effective in very low concentrations.

Acetylcholine, $\text{CH}_3\text{COOCH}_2\text{CH}_2\text{N}(\text{CH}_3)_3\text{OH}$, is a relatively simple substance which is liberated by various types of nerves and is physiologically active in very minute amounts.

Adrenaline, $(\text{HO})_2\text{C}_6\text{H}_3\text{CHOHCH}_2\text{NHCH}_3$, has already been mentioned earlier (p. 484). It is found in the adrenal glands (medulla) and is thought to be the hormone liberated by this portion of the gland. The use of adrenaline as a drug in medicine in alleviating asthma attacks and with local anesthetics to prevent bleeding rather overshadows its activity as a hormone. There is not general agreement as to the normal functions of adrenaline, itself, in the body. It does not appear to be essential to life.

The cortex of the adrenal gland produces regulatory substances which are essential to mammalian life. Among the physiologically active principles isolated from this portion of the gland is **corticosterone**.

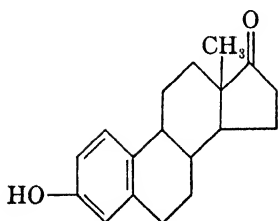


Corticosterone

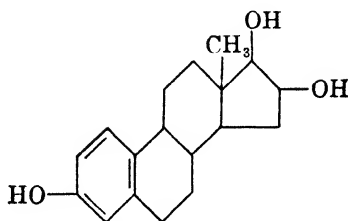
It should be noted that this compound possesses two ketone groups, two alcohol groups, and a ring structure like that in cholesterol. A number of related compounds have also been found with varying physiological activity but their actions are too complex to discuss here.

Sex Hormones. Before corticosterone and other cortical hormones were discovered various sex hormones which are closely related chemically (and also physiologically in some cases) were known.

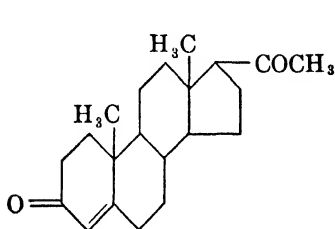
Among these the best known are **estrone**, **estriol**, **progesterone**, **androsterone**, **dehydroandrosterone**, and **testosterone**. Their abbreviated formulas are given below.



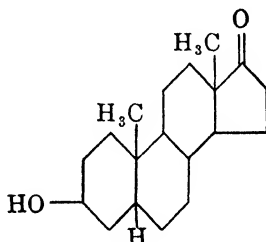
Estrone (theelin)



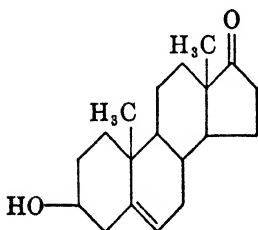
Estriol (theelol)



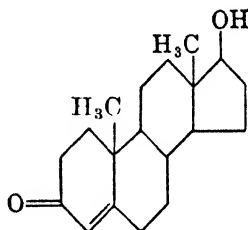
Progesterone



Androsterone



Dehydroandrosterone



Testosterone

The first three above are classed as *female* sex hormones and the latter three as *male* sex hormones. The situation is not as simple as this classification would suggest since the hormones are not limited to the indicated sex and their physiological interrelations are complicated. Their general chemical relationships to each other should be noted. As might be anticipated, there are numerous other *steroids*, many of which are synthetic products,

which have some sex hormone activity. They differ both quantitatively and qualitatively so far as their actions are concerned.

Thyroxin has already been mentioned (p. 309) as an amino acid derivable from thyroid tissue. When administered, even by mouth, it possesses substantially the hormone activity of the thyroid gland. It appears, however, that thyroxin is not the hormone of the thyroid gland but that a protein, thyreoglobulin or something closely related, is actually secreted into the blood instead of thyroxin.

Hormones of Protein Nature. Many highly important hormones—insulin, secretin, growth hormone of the pituitary, sex hormone of the pituitary, lactogenic hormone of the pituitary, etc.—appear to be protein in nature and while some of them have been crystallized, synthesis is out of the question. It is entirely possible that simpler substances possessing structural features in common with the natural hormones will be found to possess similar hormone activity.

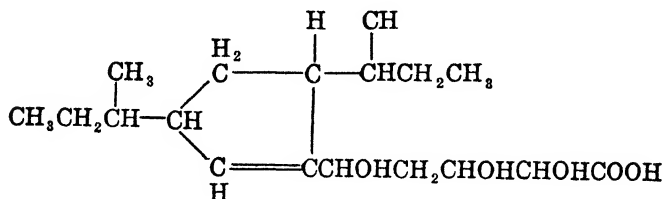
Plant Hormones

Plant hormones do not fall in exactly the same category as do the hormones of animals because they are not produced by specific glands.

Ethylene is a substance possessing distinct hormone-like properties. It is produced by plants, for example during the ripening of fruits, and in very minute concentrations induces epinasty in leaves, ripening of fruits and other effects.

Auxin is one of two similar plant hormones. A physiological test for this substance is based upon its ability when applied to one side of an oat coleoptile, to cause a lengthening of the cells on that side and a consequent bending of the coleoptile. The substance is produced by plants and serves as a growth regulator. It also occurs in animal tissues, and urine has been found to be the best source. It is characterized by its physiological activity in very high dilution. The entrance of one-millionth of a milligram of the pure substance into an individual oat coleoptile causes a bending of about 25°. Although a total of less than a gram of the crystalline material has been obtained, by using microanalysis

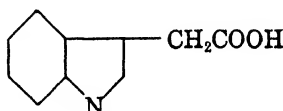
(p. 6) and other micro methods its chemistry has been worked out and the following formula assigned to it.



Auxin a (Kögl)

Auxin *b* is closely related chemically and physiologically.

Wholly unrelated chemically is a group of substances which strangely possess physiological activity similar to the auxins. The first compound of this type to be recognized, heteroauxin, was indole acetic acid which is produced in mold cultures.



Heteroauxin

Numerous other acids of synthetic origin have been found to possess hormone activity in varying degrees and similar to indole acetic acid. Prominent examples are indole butyric acid, 2,4-dichlorophenoxy acetic acid (2,4-D) and α -naphthalene acetic acid but there are many others. 2,4-D is used extensively as a weed killer while α -naphthalene acetic acid is sold under a number of different trade names to be used to delay the falling of apples when they ripen.

Traumatic Acid. This "wound hormone" is produced as a result of injury of the tissues of bean pods and functions in connection with the new growth which is produced. It has recently been isolated and synthesized. Its structure is given below



Traumatic Acid

Enzymes

These special biochemical catalysts which are of fundamental importance in biochemistry have been studied intensively in recent years and found to be protein in nature. Not only have a number been isolated in crystalline form but information has been obtained in many cases as to the constituent chemical groups which are associated with the catalytic activity. B vitamins are often involved. To pursue this and similar subjects further would take us too far into the field of biochemistry.

CHAPTER XXXIX

SPECIAL PHYSICO-CHEMICAL METHODS IN ORGANIC CHEMISTRY

Certain physico-chemical principles such as those involving molecular weight determinations, ionization, atomic structures, etc., enter necessarily into the elementary study of chemistry whether dealing with inorganic or organic compounds. We have already had occasion to mention these and certain other applications of physical chemistry such as optical rotation, heats of formation and combustion, and reaction rates, which have a particular importance in organic chemistry. As a matter of fact practically every physical-chemical method has its applications in organic chemistry, and physical chemistry divorced from all its organic applications would be greatly diminished in scope.

There are certain tools of physical chemistry (many of rather recent development) which are so fundamental to a modern study of the structure of organic molecules that space is taken here for a very elementary discussion of their possibilities. As has been emphasized continuously throughout this text, the determinations of molecular structures and the evidence on which these structures are based are of central importance. This evidence, especially as regards more complex compounds, cannot be appreciated in many cases without at least an elementary knowledge regarding the topics discussed briefly in the following paragraphs.

Absorption Spectra. In the discussion of color in relation to constitution some elementary conceptions were outlined. Colored substances have characteristic absorption spectra in the visible region. Substances with related structures have *similar* but not identical absorption spectra. Therefore the identity of two colored substances from different sources can be ascertained by a study of their absorption spectra. It is on the basis of this evidence that it is concluded that the colored part of hemoglobin molecules (prosthetic group, p. 321) is the same from different

animals though the hemoglobins themselves as a whole differ greatly in crystal form, etc. Evidence of identity based upon absorption spectra is of questionable value unless the degree of dispersion used is large. Otherwise there may be small differences in absorption spectra which the instrument does not reveal. Unfortunately ordinary absorption spectra are largely empirical and it is not in general possible to calculate in advance what the absorption spectrum of a compound of known structure will be like.

Ultra-Violet Absorption Spectra. Since the majority of organic compounds are colorless (in the visible region), the ultra-violet region where absorption bands are more likely to occur, can be used for their study. The same principles apply as in the visible region. Two substances will not show the same absorption bands unless they are identical and slight changes in structure lead to corresponding slight changes in the spectra, so that information of chemical interest can often be obtained by examination of the ultra-violet absorption spectra.

Infra-red Absorption Spectra. The theoretical interpretation of the infra-red absorption spectra is much more feasible than in other cases cited above. In the near infra-red region which is more often investigated, the absorption of light quanta is accompanied by changes in the vibrational and rotational states of the *molecules*. In the case of a relatively simple molecule it becomes possible to determine by the position of the absorption bands, the moments of inertia and the vibrational frequencies of the molecule. This leads to important information regarding the size and shape of the molecule. For more complex molecules the situation is complicated and the spectra cannot be analyzed completely. Infra-red absorption spectra of different organic compounds show characteristic differences and they can be used, in the same way as the other absorption spectra mentioned above. The technique is much more exacting and the infra-red absorption spectra of relatively few organic compounds have been determined.

Raman Spectra. If any transparent substance be exposed to radiation of a definite frequency then the light scattered at right angles contains frequencies characteristic of that substance and

differing from that of the incident monochromatic light. These changes in frequency are discrete, that is, the new frequencies appear at definite positions and not as gradations from that of the original frequency used. The values of these frequencies are linked up in general with the same type of rotational and vibrational factors that cause infra-red absorption. In the case of molecules that are not too complex the size and shape of the molecules and the forces required to pull the atoms apart can be calculated from the character of the spectra obtained. Definite Raman lines can be identified as being due to particular linkages within the molecule, and to certain vibrations of these links. This type of spectra is a relatively recent development. When more data are accumulated this method, largely because of relative ease of application, promises to be of more value in determining the constitution of organic compounds than any other *spectral* method.

Electric Dipole Moments. If one "end" of a molecule is positive electrically with respect to the other end (regardless of how close the ends are together), the molecule possesses a dipole moment, and in an electric field tends to orient itself. This tendency is the basis for the dielectric properties of substances and dipole measurements are based upon measurement of dielectric constants.

The results of these measurements show that such molecules as CH_4 and CCl_4 have zero moment (are non-polar), while CH_2Cl_2 is polar having a moment of 1.5 Debyes. (This unit is equal to 10^{18} E.S.U.) It is possible to determine the moments of individual linkages and in accordance with our earlier discussions a single C-H linkage has a small moment (i.e., the electrons are not held equally by the carbon and hydrogen). A C-Cl linkage has a higher moment in the opposite direction.

In *para* disubstituted benzenes there may be a moment depending on the character of the substituents and their pull on electrons. If a chlorine atom and a nitro group are substituted in *para* positions they oppose each other and the dipole moment is less than if another type of group (CH_3 for example) were present in one of the positions. In the latter case the moments

caused by both groups are in the same direction and reinforce each other.

The peculiar condition often spoken of as "coordinate valence" has an important influence on dipole moments. When carbon is attached to oxygen or nitrogen $\left(\begin{array}{c} \diagup \\ \text{C}=\text{O} \text{ or } \text{C}=\text{N}- \\ \diagdown \end{array} \right)$

there is a considerable moment, the carbon being positive. In carbon monoxide the large moment which would normally exist in carbon-oxygen double bonds is almost neutralized by the co-ordinate link ($\text{C}\equiv\text{O}$) which operates in the opposite direction to make carbon less positive. In the alkyl isonitriles the moment of the $\text{C}=\text{N}$ linkage (which is smaller than in the $\text{C}=\text{O}$ linkage) is *more* than neutralized by the co-ordinate link ($\text{C}\equiv\text{N}$) with the result that the carbon is definitely negative with respect to the nitrogen.

The measurement of dipole moments offers a method for distinguishing *cis* and *trans* isomers in some cases where direct chemical methods are not available. Thus of the two dichloroethylenes one has a zero moment; the other has a moment of about $1.9D$. It is obvious from the structures that the *trans* form is the one without a dipole moment and the *cis* form possesses the moment. Likewise the two dibromoethylenes (*cis* and *trans*) have $1.2D$ and zero moments respectively.

An interesting study of substitution on the benzene ring has been made in connection with dipole moments. It has been found possible to correlate these measurements with the directing effect of the groups in the manner outlined below. The dipole moment of toluene is $.45D$ and we may arbitrarily give it a positive sign (the CH_3 is positive with respect to the rest of the molecule which is negative). The dipole moment of methyl amine is zero, and the difference between aryl and the alkyl compounds is $+.45D$. In the case of the corresponding chlorine compounds the values are $-1.56D$ and $-2.15D$, and the difference is $+.59D$. The difference calculated in this way in the case of all *ortho-para* directing groups is, like those cited, *positive*. For $\text{C}_6\text{H}_5\text{CCl}_3$ the moment is $-2.07D$ (the substituted group is negative) while that of CH_3CCl_3 is $-1.57D$ and the difference is

$-50D$. Nitrobenzene has a moment $-3.93D$ while that of nitromethane is $-3.05D$, and the difference is $-.88D$. The *meta* directing groups in general show a *negative* difference when calculated in this way. These facts fall in line with our previous conclusion regarding the dependence of directing effects upon electron displacements. An intensive study of the phenomena, such as we shall not take space to describe here, shows, however, that the factors which govern directed substitution are too complex to be completely delineated on the basis of present knowledge regarding dipole moments.

Magnetic Dipole Moments. A magnetic field produces in every substance a diamagnetic polarization (opposing the field) as a result of the acceleration of the electrons by the field. This effect is small usually, and not of much value for structural studies. However, some substances inherently show a magnetic polarization of opposite sign (with the field). This *paramagnetic* polarization is often large and can be measured by certain magnetic methods. The permanent magnetic dipole moment of a given substance arises in part from the orbital motions of the electrons and in part from the spin magnetic moments of any unpaired electrons present. The latter factor is the more important, and from the measured magnetic dipole moment the number of unpaired electrons per molecule can be calculated.

Recently this method has been applied to studies of the dissociation of hexarylethanes into triarylmethyl free radicals. The concentration of the latter is ascertained by determining the magnetic susceptibility of the solution, the unpaired spin of the odd electron in the free radical making a paramagnetic contribution.

The application of magnetic measurements to the reactions of hemoglobin and the partial elucidation of the structure of hemochromogens and related substances has also been carried out.

Molecular Volumes—Parachors. This topic is of particular interest to us in connection with the evidence which it contributes toward the existence of coordinate links. On theoretical grounds it is to be expected that the volume occupied by a molecule would be determined in part by the types of linkages present. The experimental facts are in accord with this expectation. In order to be of the greatest value for the present purpose molecu-

lar volumes must be measured under conditions such that the large internal pressures of the liquids (such as are manifest in surface tension) are corrected for. The *parachor* is the molecular volume measured at a standard internal pressure or standard surface tension. The values of the parachor of a substance depend upon the kind and number of atoms present and the types of linkages between them. The atomic volumes (under standard internal pressure) for various elements commonly occurring in organic compounds are: C, 4.8; H, 17.1; O, 20.0; N, 12.5; S, 48.2; Cl, 54.3. The additional volume contributed by the presence of a double bond is 23.2, by a triple bond is 46.4, and by the presence of a six membered (saturated) ring is 7.7. On the basis of these experimental values it has been possible to calculate the parachors of various organic compounds which have not been previously measured. Such values check with experimental determinations usually with an error of not more than one per cent.

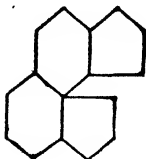
In certain compounds which, in accordance with older ideas, were formulated as possessing one or more double bonds (amine oxides, nitro compounds, sulfones), the measurement of parachors indicates that these formulas are in error and that "coordinate valences" (and resonance) replace certain of the double bonds (p. 215). In the case of amine oxide, for example, the correct parachor is found by addition of the volume contributions of the various atoms, *not* by the addition of 23.2 for the presence of a double bond, but rather by the subtraction of a small amount (1.6) which is found in a number of cases to be approximately the volume effect of the "coordinate valence." The determination of parachors is thus a very important method of determining the presence of so-called coordinate links.

The *molecular solution volumes* of soluble organic compounds can of course be measured and they have been made use of by Riiber (Tids. Kjeimi Bergvesen 12, 227-44, 1932 [in English]) in the study of the configurations of sugars. Molecular refractions were also used in the same connection and have been used extensively, principally by Dutch workers for the study of various structural problems that cannot be handled readily by ordinary chemical means. The value of such methods increases as more and more data accumulate. With a large body of data to

use for comparison experimental values may be interpreted which otherwise would be meaningless.

X-ray Diffraction. We cannot take space here to discuss the principles of diffraction and interference as applied to radiant energy. It is obvious to those who have dealt with this subject that if the wave length of the radiation is known the dimensions of the "grating" can be calculated on the basis of the diffraction pattern obtained. This principle has been used extensively in the determination of crystal structure by x-ray diffraction since the crystal lattice behaves like a grating for the x-rays, which have very short wave lengths compared to light.

In the crystals of organic compounds (other than salts) the units of which the crystals are built are molecules. It is therefore possible by complex mathematical analysis of the diffraction patterns (obtained by the use of x-rays of known frequency) resulting from the crystal of an organic compound, to calculate the shape and dimensions of the molecules as well as the manner of arrangement in the crystal. We know from various types of study (molecular volumes, x-ray diffraction, Raman spectra, etc.), especially of simpler molecules, the dimensions of atoms, so that models can be constructed representing any desired organic structure. If such a model cannot be fitted into the space which x-ray evidence indicates each molecule occupies in the crystal, the structure must not represent the substance in question. The related structures of calciferol, ergosterol and cholesterol (p. 403) have been revised on the basis of x-ray evidence. It was found that the calciferol molecule must occupy a space $5 \times 7.2 \times 17\text{-}20\text{\AA}$, but that it could not have as little width and depth and be as long as this, and have the more compact formula involving the ring system pictured below. (This was previously supposed to be present in all three sterols mentioned above.)



As a result of this serious discrepancy as well as chemical difficulties the accepted ring structure was suggested which appears to meet the chemical difficulties as well as those encountered in x-ray investigation. It may be noted also in this connection that the structure ascribed to ascorbic acid (vitamin C) which has been proved correct by synthesis, was arrived at in part by x-ray diffraction studies of the crystals.

The number of applications of x-ray studies to organic chemistry is so large that we can only give a few hints as to their importance. Those studies dealing with cellulose and other fibers are of outstanding importance since many of the problems are so difficult to attack by chemical means. By study of x-ray diffraction patterns it becomes clear that in fibers, molecules are oriented (i.e., stretched out) so that they lie parallel to the fiber axis. In unstretched rubber the molecules lie in random directions but become oriented on stretching. We have already mentioned the x-ray evidence regarding the dimensions of the units of which cellulose (and also rubber) molecules are composed.

X-ray diffraction can even be applied to substances in the gaseous state. Although the molecules are in random positions and orientations, diffraction patterns are obtained in the form of concentric halos of varying intensity and radii, which are capable of mathematical analysis. Long exposures are necessary because of the small amount of diffraction caused by the relatively few molecules present in a gas.

Electron Diffraction. It is an experimental fact that a stream of electrons appear to be diffracted in a manner similar to light or x-rays, and that a study of their diffraction by materials of known structure leads to results concordant with those obtained by x-ray study. Electrons can therefore be treated like waves, the wave length of which depends upon the speed of the electrons. By using electrons of the same speed, one obtains "monochromatic" waves which in wave length may be of the order of one twentieth that of x-rays.

Electron diffraction has some distinct advantages over x-ray diffraction especially when dealing with gases, because diffraction is much more intense in the case of electrons and very short exposures take the place of exposures of several hours which are

necessary in x-ray diffraction studies of gases. This is especially advantageous in dealing with organic compounds which have low vapor pressures and thus could furnish only a low concentration of molecules in the vapor state.

The pattern obtained upon a photographic plate when a fine pencil of electrons is passed through a stream of gas, consists, as in the case of x-rays, of a dark spot in the direct path of the electrons, surrounded by concentric halos where maxima occur. The positions of these halos can be compared with the theoretical halos which may be calculated for a proposed molecular model. If they agree, the proposed model is judged satisfactory. It is remarkable that the method can be refined to such an extent that interatomic distances can be determined to an accuracy of about $\pm 2\%$ (or even $\pm 1\%$) and bond angles ascertained within limits of error of about $\pm 5^\circ$. It is also noteworthy that while there are minor discrepancies, the results of x-ray and electron diffraction studies are concordant and that the values of interatomic distances (for example) as determined by several different methods show substantial agreement.

Free Energies. We shall take very little space to discuss thermodynamic applications to organic chemistry for although potentially a very powerful tool, data have not accumulated sufficiently to make such applications extensive. Furthermore such applications require considerable background and do not bear very directly upon structure. A single illustration will serve to show the type of problem that can be solved from free energy calculations. It is supposed that at high temperature ammonia might react with benzene to yield aniline and hydrogen. From the free energies of the substances concerned it has been calculated that the equilibrium in the reaction is such that even at high temperature (which would be favorable since the reaction is endothermic) at most very little aniline would be formed. Free energy calculations cannot reveal the speed at which equilibria in a given reaction may be established, but they can at the outset determine what reactions are thermodynamically impossible, provided the free energy data necessary for the calculations are available.

Use of Isotopes in Organic Chemistry

One of the most important developments in organic chemistry in recent years has been the use of tracer elements in the study of the mechanism of chemical reactions, problems related to plant and animal metabolism and in the treatment of disease. These tracer or tagged elements are the radioactive and the stable heavy isotopes of the common elements, many of which have recently become available as a result of research related to nuclear fission. These isotopes have two properties which make their use possible: (1) all isotopes of an element have the same chemical reactions and (2) both the radioactive and the stable heavy isotopes can be detected in very low concentrations. A small amount of radioactive isotope mixed with a much larger amount of the corresponding common non-radioactive element will serve to "trace" or "tag" the behavior of the latter. Not only can the presence of these radioactive isotopes be detected but instruments have been developed for their quantitative measurement and these methods are much more rapid and convenient than typical chemical analysis.

Fortunately for the organic chemist, there are now available tracer isotopes of all the elements common to organic compounds. The following table gives a list of the isotopes of some of the more important elements.

The choice of whether to use a stable isotope or a radioactive isotope is governed by several factors besides availability. With radioactive isotopes the half-life of the isotope and the nature of the radiations are the main considerations. For certain biological work the radiations may be harmful but for diagnostic and curative medicine they may be invaluable. An advantage in the use of radioactive tracers lies in the fact that the instruments used for the counting of their radiations are so sensitive that only very small amounts need be present. Radioactive carbon C^{14} , for example, can be detected in a dilution of 10^8 . The stable heavy isotopes are analyzed by the mass spectrograph which utilizes the differences in weight between them and the ordinary isotopes. It is not possible to analyze for heavy isotopes in such great dilution as with radioactive ones. Heavy carbon

TABLE OF ISOTOPES¹

Element	Mass Number	% Abundance in Nature	Type of Radiation	Half-life
H	1	99.98	Stable
D	2	0.02	Stable
T	3	β^-	31 yr.
C	10	β^+	8.8 sec.
	11	β^+	20.5 min.
	12	98.9	Stable
	13	1.1	Stable
	14	β^-	6100 yr.
N	13	β^+, γ	9.93 min.
	14	99.62	Stable
	15	0.38	Stable
	16	β^-	8.0 sec.
O	15	β^+	126 sec.
	16	99.76	Stable
	17	0.04	Stable
	18	0.20	Stable
	19	β^-	31 sec.
Na	21	?	23 sec.
	22	β^+, γ	3.0 yr.
	23	100	Stable
	24	β^-, γ	14.8 hr.
	25	β^-, γ	62 sec.
P	29	β^+	4.6 sec.
	30	β^+	2.55 min.
	31	100	Stable
	32	β^-	14.30 days
S	31	β^+	3.2 sec.
	32	95.1	Stable
	33	0.7	Stable
	34	4.2	Stable
	35	β^-	87.5 days
	36	0.016	Stable
I	124	β^+	4.0 days
	126	β^-, γ	13.0 days
	127	100	Stable
	128	β^-, γ	24.99 min.
	130	β^-, γ	12.6 hr.
	131	β, γ	8.0 days
	133	β^-	22 hr.
	135	β^-	6.6 hr.

¹ Adapted from table of isotopes published by G. T. Seaborg, *Reviews of Modern Physics*, 16, 1 (1944).

has not been analyzed below about a 0.01 per cent concentration.

There follows a brief discussion of the various isotopes of hydrogen, carbon, nitrogen and oxygen. Of these only deuterium has been available for a period of years and it will be discussed in more detail than the others. In general, the principles which apply to deuterium also apply to the isotopes of the other elements.

Isotopes of Hydrogen. An advance in physical chemistry which has taken place recently and which has made very important contributions to organic chemistry is the discovery and isolation of the stable heavy isotope of hydrogen with an atomic weight of 2 (deuterium, D^2). In general isotopic forms of elements are chemically practically indistinguishable but in this case there is such a large variation in the mass (a doubling) that this is accompanied by some change in chemical properties. A third isotope of hydrogen (tritium, T^3) has also been produced. This isotope is radioactive with a half-life of 31 years. The radiation from this isotope is, however, too soft to be readily measured, thus deuterium is usually used for tracer work. Deuterium is available in a purity of 99.9 per cent.

The interesting possibilities in organic chemistry center around the fact that by physical means it becomes possible to distinguish between two hydrogen atoms within the same molecule, if one is deuterium and the other ordinary hydrogen. By the application of this principle it has been possible to solve (or partially solve) problems regarding reaction mechanisms and tautomerism, and further extensive investigations along this as well as other lines are to be expected.

Secondarily, the existence of a second kind of hydrogen multiplies the number of theoretically possible organic compounds many times. There are thus theoretically five different methanes with 0, 1, 2, 3, and 4 of the hydrogen atoms replaced by deuterium. Similarly there are 10 ethanes and 30 propanes. When one considers the possible substitution products of these, the number of derivatives of the first three members of the paraffin series alone becomes stupendous. Among the aromatic hydrocarbons there are 13 possible benzenes and some 76 possible naphthalenes, each capable of yielding at least as many deriva-

tives as the ordinary hydrocarbons. The total number of possible compounds is, of course, even much greater than given here; the use of tritium has not been considered and carbon also has a number of isotopes.

The mere discovery of new compounds has never been a serious problem for the organic chemist, and if the discovery of "heavy" hydrogen merely resulted in the recognition of a vast number of new organic compounds it could hardly be regarded as fulfilling a "long felt want."

However, the discovery of deuterium has already contributed something to our understanding of the behavior of already known compounds and in the future it is likely to contribute much more. One of the first illuminating discoveries of significance to organic chemistry is the fact that when hydroxyl compounds are dissolved in heavy water (deuterium oxide), the hydroxyl hydrogens are immediately displaced with deuterium from the heavy water. Ammonia behaves in the same way and amino compounds in general must be expected to behave likewise. Hydrogen which is attached to carbon (except in the case of acetylene) is, however, not displaced. This is in line with the conceptions developed in the earlier portions of this book. Hydroxyl and amino compounds have a slight tendency to ionize. This ionization though it may be very slight is very rapid and an interchange takes place immediately. With paraffin hydrocarbons there is no ionization and no replacement.

Not only do well authenticated hydroxyl compounds such as glycol and sucrose exchange all their hydroxyl hydrogen freely with deuterium from heavy water, but substances capable of existing in enol forms also exchange more or less rapidly. This promises to be a fruitful method of studying enolization. Experiments with acetone in acid or neutral solution show that the interchange takes place slowly but that in potassium carbonate solution the hydrogen is replaced by deuterium much more rapidly. This is in accordance with our previous discussion of the enolization of acetone as affected by an alkaline medium.

Even in acetic acid and its salts there is some evidence of enolization which, however, is at most very slow. Acetic acid with heavy water yields immediately deuterio-acetic acid, which has

an ionization constant about one third that of ordinary acetic acid. On standing for a long time in heavy water acetic acid and acetates may have the hydrogen of the methyl group partially replaced presumably by enolization.

The mutarotation of glucose in heavy water has been studied and found to be much slower than in pure water. The only reasonable interpretation of this fact is that the reaction involves the migration of heavy hydrogen (replaced hydroxyl hydrogen) from the alcoholic group to the aldehyde group as pictured on page 345.

The study of the Raman spectra of deuterio-alcohols and deuterio-chloroform has made it possible to assign certain Raman frequencies to definite atomic vibrations and to settle points on which there has been doubt previously. Heavy hydrogen is a tool which is certain to find extensive use in the field of organic chemistry.

Isotopes of Carbon. There are available both radioactive and stable heavy isotopes of carbon suitable for biological and organic research. In the spring of 1947 the stable isotope (C^{13}) could be obtained in a 20 per cent concentration and the only useful radioactive isotope (C^{14}) was sold in a 3 per cent concentration as barium carbonate. "Carbon fourteen" is also a stable isotope for all practical purposes because its half-life is 6100 years. The radiations are soft and no particular precautions are needed in working with this isotope. The methods of analysis and limits of dilution for these isotopes have already been mentioned (p. 622). Analysis involves determining the heavy isotope content of the carbon dioxide obtained by oxidation.

Because these isotopes are available as carbon dioxide, their introduction into organic molecules usually involves one of the standard organic synthesis such as the reaction between carbon dioxide and a Grignard reagent. The use of this carbon dioxide in plant syntheses is not very practical because too many different things are produced, mostly ones not desired. Some work has been done, however, on photosynthesis and it is expected that this great secret of nature will be unlocked by tracer chemistry. Since these isotopes have become available only recently not a great quantity of research using them has been reported

as yet. The use of radioactive carbon probably will be the choice of organic and industrial chemistry while the stable isotope will be used in biological chemistry.

Isotopes of Nitrogen. Both radioactive nitrogen (N^{13}) and a stable heavy isotope of nitrogen (N^{15}) have been produced. Radioactive nitrogen has such a short half-life that a one-hour experiment is about the longest possible. The stable isotope is available in a 60 per cent concentration (1947) and is introduced into organic molecules as ammonia through Gabriel's synthesis and other syntheses involving ammonia.

The heavy isotope content of the nitrogen obtained by the oxidation of ammonia from the Kjeldahl decomposition of the organic compound is determined by the mass spectrograph. Concentrations as low as 0.003 per cent can be detected.

Isotopes of Oxygen. Very little work has been done with the isotopes of oxygen. The most promising is the stable heavy isotope O^{18} which can be introduced into an organic molecule by reactions involving water containing the isotope. The mechanism of the esterification reaction has been elucidated by the use of O^{18} .

APPENDIX I

NUMERICAL ANSWERS TO PROBLEMS

CHAPTER I

1. M.W. 297.
2. M.W. 191.
3. (a) 133° , Δ benzene -368° , Δ acetic acid -293° ; water sol. B.P. -100.039° ; benzene sol. B.P. $80.4^{\circ} + .201^{\circ} = 80.601^{\circ}$; acetic acid sol. B.P. $118.7^{\circ} + .190^{\circ} = 118.890^{\circ}$.
5. 42.16° .
6. 284 mm. Hg., 356. H_2O , F.P. $-.031^{\circ}$.
7. $\text{C}_4\text{H}_3\text{O}_3$, $\text{C}_4\text{H}_3\text{O}_3$.
8. CH_2S .
9. M.W. 60.
10. M.W. 893.
11. 24.23 cc.
12. C, 5.34; Cl, 22.69; Br, 25.62; F, 17.12.

CHAPTER II

3. C_3H_8 , 81.81% C, 18.19% H.
 C_4H_{10} , 82.76% C, 17.24% H.
 $\text{C}_{32}\text{H}_{66}$, 85.33%, 14.67% H.
 $\text{C}_{35}\text{H}_{72}$, 85.37%, 14.63% H.
5. (a) 60 cc., (b) 50 cc.
6. $n/2$.
7. 10 parts CH_4 , 5 parts C_2H_6 .
9. 8, 26, 14, 20, 8, 8.
10. 12.

CHAPTER III

5. 10.

CHAPTER IV

4. 5.709 g., 0.860 g.
5. C_3H_6 .
8. 40 cc., 10 cc.
11. 68 Cal.

CHAPTER V

2. 1.849 g.
6. 695 cc.
7. 7.13 g.
8. 45.9.
9. 412 liters.
10. 1.25 liters.

CHAPTER VII

2. 49.3 g., 18.5 g.
9. 74 g., 394 g.

CHAPTER VIII

1. 65%.
3. 1120 cc.
4. 25.16 kg.
9. 16.01 g.
11. 256.

CHAPTER X

5. 39.6 g.

CHAPTER XI

1. 70.4 ml.
2. 76.98%.
3. 59.

CHAPTER XIII

4. Six.

CHAPTER XV

2. C, 49.5% ; H, 6.5% ; O, 44.0%.
5. $3\frac{5}{8}$ gm. mol.

CHAPTER XVI

4. (a) 111.1 ml.; (b) 59 ml.
6. 5.43 g.
7. 249.0 cc.
9. 0.90 g.

CHAPTER XVII

1. 3.86° .

CHAPTER XX

1. 89.
4. 98.6%, 97%, 110.3%.
6. 9.4 liters CO_2 , 2.07 g. urea, 7.55 g. H_2O .

CHAPTER XXI

3. 2.19 g.
6. 1050 cc.
7. Three, excluding rhamnose.

CHAPTER XXII

1. (a) 0.587 g.; (b) 4.70 g.
6. 32%.

CHAPTER XXIV

7. 16.6 g.

CHAPTER XXVI

3. 23.1 g.
7. 41.4 cc.

CHAPTER XXVII

1. 104 cc.
5. 44.
6. 335 ml.
9. 26.4 cc.

CHAPTER XXVIII

8. 0.434 g. ; 28.7%.

CHAPTER XXIX

1. 102.5 ml.
4. 314.
5. Nine.

CHAPTER XXXII

1. Six.
4. Three.

CHAPTER XXXIII

3. Twelve.

CHAPTER XXXIV

2. 94.74%, 95.24%.

CHAPTER XXXV

2. 25,400,000 lbs.
4. 616,000 lbs.

CHAPTER XXXVI

7. 96.2.

CHAPTER XXXVII

5. 289.

APPENDIX II

CONSULTATION OF THE CHEMICAL LITERATURE

The consulting of chemical literature is an important part of the work of a chemist and the task of learning how to find the desired information with the least expenditure of time is not easy. Before any research is undertaken a thorough search of the literature should be made, otherwise the entire time may be wasted in duplicating what has already been done or attempted.

It is never possible to make a proper search of the literature without consulting periodicals in foreign languages, principally in German and sometimes in French. It may be necessary at times to consult articles in Italian, Spanish, Swedish, Russian, or some other modern language but for ordinary purposes English, German and French are sufficient. For the encouragement of the prospective chemist it should be stated that the reading of journal literature in foreign languages often does not require special linguistic ability. The terminology in different languages is similar and in many cases identical, and the language is often very simple. It is more difficult to obtain a reading knowledge of German than of French. Special books and dictionaries have been published which have helped many chemical students with the language difficulty.¹

We will first consider the case in which it is desired to get the available information about a particular compound. If only incomplete information is desired, it may be found in some of the text books in English, none of which, however, is comprehensive. The largest and most complete work in English is a three-volume translation of Richter's "Organic Chemistry." A more recent reference book is Heilbron's Dictionary of Organic Compounds (3 vols.). When complete information is desired, Beilstein's

¹ Greenfield, "Chemical German," D. C. Heath & Co. Patterson, "German-English Dictionary for Chemists," John Wiley & Sons. Dolt, "Chemical French," Chemical Publishing Co. Patterson, "French-English Dictionary for Chemists," John Wiley & Sons.

"Organische Chemie" (preferably the fourth edition) should first be consulted. If the German name of the compound in question is known, it may be found in the index of the proper volume of Beilstein.² If only the structural formula of the compound in question is known, this is converted into its molecular formula which can then be found in Richter's "Lexikon der Kohlenstoff Verbindungen" or the supplementary work Stelzner's "Literatur-Register der organischen Chemie." These works refer to Beilstein and the latter especially gives many references to the periodical literature.

Beilstein's "Organische Chemie" is of the nature of an encyclopedia of organic chemistry, except that the related compounds are grouped into families and are not listed alphabetically. Very brief information regarding the compounds is given along with numerous references to the journal articles in all languages. Beilstein's work is consulted so frequently that it is sometimes jokingly referred to as the "Bible" of the organic chemist. When the articles referred to by Beilstein are consulted, references to other articles will also be found. In this way much of the literature concerning a given compound can be located.

The search for articles will ordinarily be complete after the recent indices of "Chemisches Centralblatt" and of "Chemical Abstracts" which date from 1907 to the present are consulted. It is a matter of judgment and opinion how many years back one should consult the literature. These are abstract journals, and give short synopses of journal articles which have been printed in all languages. Especially for recent years "Chemical Abstracts" may be considered complete, and for these years the "Centralblatt" need not be consulted. The number of journals from which abstracts are made for "Chemical Abstracts" is nearly one thousand, covering all branches and applications of chemistry. This shows how important and indispensable this abstract journal is. The system of nomenclature adopted by "Chemical Abstracts" and widely used is discussed in the front of the

² E. H. Huntress' Introduction to the Use of Beilstein (J. Wiley) may be consulted with profit.

Decennial Indices and more fully in the Journal of the American Chemical Society, **39**, 1623 (1917), in Science, **87**, 215-6 (1938) and in the Introduction to the 1945 Subject Index, Chemical Abstracts, **39**, 5867-5975.

If information is desired about a certain topic rather than about a particular compound, the problem is more difficult, and the best method of procedure will depend somewhat upon the character of the topic. References have been cited in the text to numerous books where special topics are treated. For discussions of reactions and the relationships of compounds, etc., the student should consult "Organic Reactions" (3rd vol., 1946) and Meyer-Jacobson, "Lehrbuch der Organischen Chemie" (bound in six volumes). For the discussion of laboratory methods "Organic Syntheses" (27th vol., 1947) and Houben-Weyl, "Die Methoden der Organischen Chemie" (four large volumes) are invaluable. Aside from the numerous elementary texts, there are several more advanced books of a general nature in English which will prove very valuable to the student. These include Gilman, "Organic Chemistry, An Advanced Treatise"; Whitmore, "Organic Chemistry"; Stewart, "Recent Advances in Organic Chemistry"; Waters, "Physical Aspects of Organic Chemistry"; Branch and Calvin, "The Theory of Organic Chemistry"; Remick, "Electronic Interpretations of Organic Chemistry"; Wheland, "The Theory of Resonance"; Mulliken, "Identification of Pure Organic Compounds" and Pauling, "The Nature of the Chemical Bond," 2nd ed.

In obtaining full information on any topic the "Chemisches Centralblatt" and "Chemical Abstracts" should be consulted. The "Industrial Arts Index" is also often valuable especially where general information is required. It is well in consulting the indices to look up, not only the particular topic under consideration, but also other related topics.

We have not gone into detail concerning the consultation of chemical literature. For further information on this matter the student is referred to Reid, "Introduction to Organic Research" (D. Van Nostrand Co.), which also contains much other valuable material.

APPENDIX III

<i>English</i>	<i>German</i>	<i>French</i>
Carbon	Kohlenstoff	Carbone
Hydrogen	Wasserstoff	Hydrogène
Oxygen	Sauerstoff	Oxygène
Nitrogen	Stickstoff	Azote
Sulfur	Schwefel	Soufre
Hydrocarbon	Kohlenwasserstoff	Hydrocarbure
Methane	Methan	Méthane (formène)
Ethyl Alcohol	Weingeist	Alcool éthylique
Acetylene	Acetylen	Acétylène
Formic acid	Ameisensäure	Acide formique
Acetic acid	Essigsäure	Acide acétique
Ethyl iodide	Athyljodid	Iodure d'éthyle
Methylamine	Methylamin	Méthylamine
Ether	Äther	Oxyde d'éthyle
Ethyl acetate	Essigsäureäthylester	Éther acétique
Sodium acetate	Essigsäures Natrium	Acétate de sodium
Formaldehyde	Formaldehyd	Formaldéhyde
Oxalic acid	Oxalsäure	Acide oxalique
Succinic acid	Bernsteinsäure	Acide succinique
Tartaric acid	Weinsäure	Acide tartrique
Lactic acid	Milchsäure	Acide lactique
Fat	Fett	Graisse
Sugar	Zucker	Sucre
Protein	Eiweiss	Albumine
Terpene	Terpen	Terpine
Benzene	Benzol	Benzène
Nitrobenzene	Nitrobenzol	Nitrobenzène
Azobenzene	Azobenzol	Azobenzène
Benzaldehyde	Benzaldehyd	Benzaldehyde
Salicylic acid	Salicylsäure	Acide salicylique
Phenolphthalein	Phenolphthalein	Phenolphthaléine
Sulfuric acid	Schwefelsäure	Acide sulfurique
Nitric acid	Salpetersäure	Acide azotique
Nitrous acid	Salpetrige Säure	Acide azoteux
Glycerol	Glyzerin	Glycérine

APPENDIX IV
PRODUCTION FIGURES

VARIOUS SYNTHETIC ORGANIC CHEMICALS 1947

	Pounds	Price per lb.
Acetanilide, tech. and U. S. P.	8,000,000	0.19
Acetic acid:		
Synthetic	370,000,000	0.11
Recovered	1,400,000,000	
Natural	24,000,000	
Acetic anhydride	600,000,000	0.14
Acetone	390,000,000	0.10
Aniline	105,000,000	0.13
Butyl alcohol, primary, normal	145,000,000	0.32
Carbon tetrachloride	200,000,000	0.07
Chlorobenzene, mono	323,000,000	0.07
Dibutyl phthalate	22,000,000	0.34
Ethyl acetate (85%)	83,000,000	0.18
Ethylene glycol	210,000,000	0.14
Ethyl ether, tech. and U. S. P.	42,000,000	0.11
Formaldehyde (37% by weight)	523,000,000	0.04
Methanol:		0.04
Natural	16,000,000	
Synthetic	537,000,000	
Phenol (synthetic and natural) tech. and U. S. P.	258,000,000	0.13
Phthalic anhydride	137,000,000	0.18
Styrene (Government and privately owned plants combined)	240,000,000	
Tricresyl phosphate	11,000,000	0.33

SYNTHETIC MEDICINALS

Aspirin	12,000,000
Phenolbarbital	440,000
Sulfa drugs:	
Sulfathiazole	2,900,000
All other sulfa drugs	4,400,000

PERIODIC CLASSIFICATION OF THE ELEMENTS																		
The atomic numbers are placed above the symbols of the elements; the atomic weights below the symbols.																		
Group	Ia	IIa	IIla	IVa	Va	VIa	VIIa	VIII	Ib	IIb	IIIb	IVb	Vb	VIb	VIIb	0		
Type	R ₂ O RH	RO RH ₂	R ₂ O ₃	RO ₂	R ₂ O ₃	RO ₂	R ₂ O ₇	RO ₄	R ₂ O	RO	R ₂ O ₃	RO ₂ H ₂ R	R ₂ O ₃ H ₂ R	RO ₃ H ₂ R	R ₂ O ₇ HR	Inert Gases		
Period 1 2 Elements	1 H															2 He		
Period 2 8 Elements	3 Li	4 Be														10 Ne		
Period 3 8 Elements	11 Na	12 Mg														18 Ar		
Period 4 18 Elements	19 K	20 Ca	21 Sc	22 Ti	23 V	24 Cr	25 Mn	26 Fe	27 Co	28 Ni	29 Cu	30 Zn	31 Ga	32 Ge	33 As	34 Se	35 Br	36 Kr
Period 5 18 Elements	37 Rb	38 Sr	39 Y	40 Zr	41 Nb	42 Mo	43 Tc	44 Ru	45 Rh	46 Pd	47 Ag	48 Cd	49 In	50 Sn	51 Sb	52 Te	53 I	54 Xe
Period 6 32 Elements	55 Cs	56 Ba	57-58-71 La	72 Hf	73 Ta	74 W	75 Re	76 Os	77 Ir	78 Pt	79 Au	80 Hg	81 Tl	82 Pb	83 Bi	84 Po	85 At	86-88 Rn
Period 7 Fr	87 Fr	88 Ra	89-90-96 Ac															(222) Rn
Transitional Elements																		
Atomic weights below the symbols.																		
Atomic weights below the symbols.																		

*Rare Earth Elements (Lanthanide Series) Group IIIa																											
58 Ce	59 Pr	60 Nd	61	62 Sm	63 Eu	64 Gd	65 Tb	66 Dy	67 Ho	68 Er	69 Tm	70 Yb	71 Lu														
140.13	140.92	144.27		150.43	152.0	156.9	159.2	162.46	164.94	167.2	169.4	173.04	174.99														
**Actinide Series Group IIIa																											
90 Th	91 Pa	92 U	93 Np	94 Pu	95 Am	96 Cm																					
232.12	231	238.07	(237)	(239)	(242)	(243)																					

A modification of a chart printed in the *Journal of Chemical Education*.

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